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on

THE RELATION OF VARIOUS PATHOLOGICAL STATES IN MAN
TO SENSITIZATION TO FOREIGN PROTEINS, WITH SPECIAL
REFERENCE TO DISEASES OF THE SKIN.

by

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I. INTRODUCTORY REMARKS ON THE HISTORY AND
PRESENT IMPORTANCE OF THE SUBJECT.

Throughout the ages it has been recognised that certain individuals have an idiosyncrasy for particular articles of food such as eggs, shell-fish, or strawberries, and that the ingestion of them would unfailingly be followed by various toxic manifestations, such as gastro-intestinal disturbance or urticaria. This observation has been crystallized in the well-known Scots proverb that "Ae man's meat is anither man's poison".

In more recent times John Hunter described "the flushing and erysipelatous inflammation of the skin" that occurred in some individuals after eating strawberries. In 1839 Magendie observed that eggs were toxic to certain people. Jenner also noticed an individual idiosyncrasy to certain common articles of food. Modern text-books on Medicine and Dermatology give long lists of articles of food which have
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at various times been found to be responsible for toxic manifestations in certain individuals, and the success achieved in particular cases by the elimination of certain articles from the dietary has no doubt been responsible for the vogue that certain systems of diet have enjoyed from time to time. The phenomenon has usually been ascribed to an idiosyncrasy or idiopathy, and it is only since the beginning of the present century that any attempt has been made to explain the underlying mechanism or to find a cure for the condition.

A parallel is found in the case of Hay Fever which had long been a puzzle to physicians. It's seasonal recurrence was first recognized by Bostock in 1819, but it was not till 1873 that Blackley of Manchester wrote the first good account of the affection, and submitted evidence that it was caused by the pollen of certain grasses, and especially the Rye grass. Following on this, Marsh of New York proved the "Fall Fever" of America to be due to the pollen of Ragweed and in 1885 Morell Mackenzie asserted that Hay Fever was not associated with any morbid condition of the nose and was entirely due to an idiosyncrasy to pollens.

After the birth of Serology in the last decade
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of the 19th Century, Dunbar of Hamburg, using a watery extract of various grass pollens, was able in 1903 to prove that they contained a toxin, against which a specific antitoxin was developed in the blood of the injected animal. He also demonstrated the presence of a specific precipitin and the deviation of complement in the serum of sufferers during the Hay Fever season.

In 1911 Noon¹ and Freeman² published papers on the immunization of Hay Fever patients with injections of grass pollen extracts.

In 1894 Behring and Kitasato introduced as a therapeutic measure the passive immunization of Diphtheria sufferers with the antitoxic serum of the immunized horse and the medical profession became familiar with the phenomena of Serum Sickness.

When in 1902 Chas. Richet observed the phenomenon of Anaphylaxis, there was a tremendous development of interest in the effects of introducing foreign proteins into the living organism, and Von Pirquet and Schick recognized in Serum Sickness the occurrence of Anaphylaxis in the human subject. In 1906 Langlois³ suggested an anaphylactic origin for Hay Fever, and in/

1. Lancet. June 10. 1911.

2. Lancet. Sept. 16. 1911.

3. Presse Médicale. Paris. 1906. XLV: 583.

in 1907 Wolff Eisner⁴ pointed to the analogy between Urticaria, Hay Fever, and Serum Disease, and was the first to suggest that Urticaria could be explained on the ground of hypersensitiveness to foreign protein.

In 1909 Auer and Lewis of the Rockefeller Institute, and in 1910 Theobald Smith, showed that the lung of an anaphylactic guinea-pig has all the characteristic appearances of a case of Bronchial Asthma, and Meltzer⁵ wrote on Asthma as a phenomenon of anaphylaxis. In 1910 Fordyce⁶ at the Annual Meeting of the American Dermatological Association suggested that Eczema might be anaphylactic in origin and at the next annual meeting of the same association he extended the suggestion to the case of the Erythematosa remarking that though there was "probably a plurality of causative agents underlying the toxic dermatoses, there was no more plausible explanation of their modus operandi than that advanced by the theory of Anaphylaxis". The same theory of anaphylaxis has been brought in to explain the incubation period, eruptions, and other clinical phenomena of the exanthemata, and year by year, diseases such as Epilepsy and Migraine have been taken out of the class of idiopathies or Functional Neuroses and ascribed to the same mechanism that underlies anaphylaxis/

4. Ueber die urticaria. Vom Standpunkte der Neueren Erfahrungen. Dermatolog. Zeitschr. 1907.
5. J.A.M.A. 1910 LV. 1021.
6. Jour. Cut. Diseases 29. 129. 1911.
7. Jour. Cut. Diseases xxx. 1912. p.128

anaphylaxis. The whole subject is still obscure and involved in the dust of controversy, but a large body of responsible opinion finds expression in the words of Dr. John Thomson⁸ who writes that "There can be no doubt whatever that anaphylaxis is destined in the near future to play an essential part in the explanation of several morbid phenomena, which we have not hitherto been able to understand".

8. The Clinical Study and Treatment of Sick Children.
3rd Ed. p. 829.

II. THE PHYSICO-CHEMICAL CHARACTERS OF PROTEINS AND THE PHYSIOLOGY OF THEIR DIGESTION AND ASSIMILATION.⁹

Proteins form the most important constituent of living protoplasm and are essential to the vital processes in that, from them new tissues are built up in the growing plant or animal, and the processes of repair and replacement of tissue-waste, which continually occur in the living organism, are carried on.

Dale¹⁰ has pointed out that whereas the same fats and carbohydrates may be found in many different species, the distinction of species depends on the difference in their proteins which may be distinguished by their chemical or physical properties, or in closely allied species only by their immunity reactions.

Proteins belong to the class of substances known as colloids, that is, they are amorphous and most of them form a colloidal solution with water, weak saline, or dilute acids. Colloidal solutions are opalescent, exhibit the "Tyndal Phenomenon" under the ultra-microscope, exert a low osmotic pressure, do not diffuse through the membrane of a dialyser, and have a tendency/

9. Except where otherwise stated, Starling's Principles of Human Physiology, 3rd Ed., Sec. X is the authority.

10. Hexter lectures. Bulletin Johns Hopkins Hosp. 1920.

tendency to form jellies or to coagulate under the influence of heat and other simple agencies.

Under certain circumstances Proteins tend to form crystals. Haemoglobin, for example, readily crystallises. Aleurone crystals occur in nature in the Brazil nut and in the seeds of the castor oil plant and the pumpkin.

Crystals of egg-albumin and serum albumin can be obtained by the Hofmeister-Hopkins method. In all these instances, however, it is very difficult to obtain the crystals in a state of absolute purity owing to their tendency to take up other colloids which are in contact with them. For example, Haemoglobin crystals take up serum-albumin from the blood serum.

A very great variety of Protein's occurs in the animal and vegetable kingdoms and of recent years many of these have been isolated and identified.

The fact that egg-white contains five and a grain of wheat, six distinct proteins, gives some idea of the multiplicity of protein substances in our everyday/

day food. There is reason to believe that the protein molecule is of great size and complexity. It is built up, in varying proportions in different proteins of Oxygen, Hydrogen, Nitrogen, Carbon and Sulphur. Phosphorus is also present in most proteins and Iron is found in many of them.

The protein molecule is built up of a definite grouping of Amino-Acids which form its proximate constituents. So far the following Amino-Acids have been isolated:-

Glycine ; Alanine ; Serine; Amino-Valerianic Acid;
 Leucine ; Aspartic Acid; Glutamic Acid;
 Lysine ; Ornithine; Arginine; Creatine;
 Tyrosine; Phenyl Alanine; Tryptophane;
 Proline ; Oxyproline; Cystine; and Histidine.

Abderhalden, Osborne and others have done much work in investigating the molecular architecture of various Proteins and have shown that they all contain in their structure a considerable proportion of the total/

total number of Amino-Acids that have so far been identified. The difference between various proteins depends not so much on a qualitative difference in the various Amino-Acids of which they are respectively built up, as on the varying quantities of the individual Amino-Acids in one protein and another. The following table gives a few examples of the striking variations in the percentage quantities of certain of the Amino-Acids in various Proteins.

in	Percentage quantities of				
	Glutamic Acid	Glycine	Leucine	Lysine	Tyrosine
Egg Albumen	8	0	7.1	2.15	1.1
Globin	1.7	0	29	4.3	1.5
Gliadin	36.5	0.1	6	0	2.4
Gelatin	0.88	16.5	2.1	2.75	0
Caseinogen	11	0	10.5	5.8	4.5
Oats	18.4	1	15	0	1.5
Ox Muscle	15.1	2	11.1	7.1	2.2

The/

The various groups of Amino-Acids, e.g. the Mono-Amino-Acid group; the Diamino-Acid group; and the Aromatic Amino-Acid group, also show considerable differences in the relative proportions in which they occur in various proteins.

In Nature's laboratory, a foreign protein such as wheat gliadin is broken down into its proximate constituents, the Amino-Acids, and these are, under the selective action of the body cells, built up again in different order and proportions to form other protein molecules, e.g. those of muscle or blood serum, which are proper to the body.

The living organism is well-equipped for carrying out these transformations of Protein. In the vegetable kingdom the interchange of Protein between the tissues is accomplished by its disintegration into Amino-Acids and its subsequent reintegration. In the more complex processes of the Animal Kingdom, Hedin and others have shown that every tissue of the body is capable of producing intra-cellular ferments for the disintegration of the Protein molecule.

Turning now to the consideration of the normal digestion and assimilation of Proteins in man, we find that in the stomach, under the action of the hydrochloric/

Hydrochloric Acid and Pepsin of the gastric juice, the proteins of food are first brought into solution and then by the addition of several molecules of water to each protein molecule, they are converted into proteoses and Peptones. This is the initial stage of the hydrolysis of protein. The second and ultimate stage occurs in the small intestine where the Trypsin of the Pancreatic juice and the Erepsin of the intestinal mucosa reduce the Proteoses and Peptones into a mixture of Amino- Acids and a small residue of Polypeptides which consist of two or more Amino-Acids associated together.

These do not undergo further disintegration in the intestine.

The final products of intestinal digestion give no biuret reaction, showing that no proteins are left.

Animals can be maintained in good health on a protein-free diet if they are supplied with a mixture of Amino-Acids derived from the tryptic digestion of Proteins.

The question of absorption of unchanged proteins from the gastro-intestinal canal is one of great importance/

importance to our present subject.

Starling states that a small amount of Peptone may possibly be absorbed from the stomach. It is also an established fact that during the first two or three days after birth the intestinal mucosa is permeable to foreign protein. This is practically the only condition in health under which foreign protein can enter the blood-stream from the gastro-intestinal tract.

It is true that Proteoses and Peptones are, under experimental conditions, rapidly absorbed from the alimentary canal and that under ordinary circumstances a certain proportion of the products of protein digestion may be taken up in this form by the intestinal mucosa, but after even a heavy protein meal no trace of Proteose or Peptone can be found in the blood of the portal vein because, as the experiments of Cohnheim and others have proved, they are completely hydrolysed in the intestinal wall and only Amino-Acids enter the blood-stream. The absorption of appreciable quantities/

quantities of unaltered foreign protein into the blood-stream would give rise to:-

- (1) A marked fall of blood-pressure.
- (2) Alteration of the coagulability of the blood.
- (3) The appearance of albumin in the Urine.
- (4) And the repeated absorption of small quantities of unsplit foreign protein would excite the formation in the serum of a specific precipitin. Proteoses and Peptones, however, are feebly antigenic and do not induce specific antibody formation.

In most cases, however much soluble protein is ingested, none appears in the urine, and no specific precipitin can be detected in the blood serum.

Ascoli has however observed both these events after the administration of large quantities of white of egg.

Certain experiments have been carried out to prove that unaltered protein can be absorbed into the blood-stream through the intestinal mucosa.

- (1) An animal can absorb its own blood serum in an unaltered condition through a trypsin^{free} loop of small intestine.

(2)/

- (2) Friedländer found that during a period of three hours 21% of the proteins of egg white and foreign blood-serum, which had been introduced in measured quantities into a trypsin-free loop of small intestine, were absorbed.

He did not however determine the actual state of these proteins when they reached the blood-stream. Under similar conditions there was no absorption of Syntonin or of Casein.

- (3) Van Alstyne¹¹ proved with dogs that Egg-Albumen introduced into the stomach or any part of the small intestine except the duodenum passed unchanged into the blood-stream. She got the same results with ox and beef serum. She came to the conclusion that proteins may be absorbed unaltered through the intact alimentary epithelium, but that trauma favoured the phenomenon.

- (4) Arthus¹² was able to sensitize animals to protein by injecting them in solution per rectum.

(5)/

11. *The Absorption of Proteins without digestion*. *Arch. Int. Med.* Oct. 1913

12. *Quoted by Highman & Michael, Arch. of Dermat. & Syphil.* Nov. 1920.

- (5) Vaughan, Cummings, and McGlumpy,¹³ showed that rabbits absorbed foreign proteins in an unaltered state through the intestinal mucosa.
- (6) Schloss and Worthen¹⁴ isolated proteins in the urine of infants with gastro-intestinal disturbance.
- (7) Barnathon¹⁵ concluded that absorption of incompletely hydrolysed proteins can occur when there is some digestive disturbance.

These findings point to the conclusion that under experimental conditions, which are not analogous to those of normal good health, and under conditions of gastro-intestinal disturbance incompletely hydrolysed proteins may be absorbed directly into the blood-stream, but they do not prove that this occurs normally to any appreciable extent, except in infants for a few days after birth.

13. "On parenteral introduction of proteids". *Ztschr. f. immunitatshf.* 9.6.1911

14. "The permeability of the gastro-intestinal tract of infants to undigested protein". *Am. Jour. Dis. Childr.* May 1916

15. "De l'anaphylaxie alimentaire". *Annales de Paris*. 1911.

III. THE SENSITIZATION OF THE BODY TO FOREIGN PROTEINS.

We have seen that under certain conditions food proteins may pass in an unaltered condition from the gastro-intestinal tract into the blood-stream. These conditions may be summarised as:-

- (1) The early days of infancy.
- (2) Gastro-enteritis from any cause, dietetic, or bacterial.
- (3) Deficient secretion of any of the digestive juices.
- (4) Great excess of protein in the diet.
- (5) Emotional disturbance in the neurotic, giving rise to temporary stasis and dilatation of the bowel, with perhaps diminution of secretion of digestive juices.
- (6) Ascarides and other intestinal parasites may produce lesions in the mucosa through which food-proteins are absorbed, or their own secretions, which are protein in character, may be absorbed into the blood-stream.

There are several other ways in which foreign proteins may enter the body.

- (1) In many infective processes both acute and chronic, such as typhoid, pneumonia, and tuberculosis, bacterial proteins enter the blood/

blood-stream either as bacteria or as bacterial toxins or as a combination of both.

- (2) In Malaria and other protozoal diseases, the blood is infested with protozoal parasites.
- (3) In cases of Hydatid cyst which rupture internally, foreign protein is set free in the tissues.
- (4) It is highly probable that various airborne proteins may be absorbed through the bronchial mucosa.

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Hektoen found that if a guinea-pig was kept in an atmosphere of sprayed serum, the serum was absorbed, presumably through the bronchial mucosa, and the animal became sensitized to the serum. It is inferred that the proteins of pollens, animal emanations, and moulds are, in the same way, absorbed through the bronchial mucosa.

- (5) Autolysis of **body** tissues may possibly in some cases result in what is practically a foreign protein. This is believed by some to occur in severe trauma, in placental degeneration and other conditions.
- (6) In modern therapeutics, large quantities of foreign protein are commonly injected both subcutaneously and intravenously, in the form of anti-toxic sera, vaccines, and solutions of Peptone.

We/

We must now consider the effect on the organism of the introduction into it in one of the above ways of foreign protein. This brings us at once to the study of immunity,¹⁷ with which we are intimately concerned. The subject is one of almost bewildering complexity, and although it has engaged the attention of many of the best brains in Science for the last three decades, it is still very imperfectly understood.

In the language of the immunologist, a foreign protein of any kind, whether derived from plant or animal, whether inherently poisonous or non-poisonous, which, when introduced into the living organism incites the formation of specific antibodies of various sorts, is termed an antigen. Examples of substances which contain one or more antigenic proteins are horse serum; bacterial vaccines; egg white; and milk.

In response to the introduction of an antigen, the mechanism of immunity is called into play, and the tissues produce various anti-bodies which are specific for each antigen. These can be detected in the blood-serum and those that have so far been isolated/

17. Delapfield & Prudden's Text book of Pathology^{11th ed.} is the authority except where otherwise stated.

isolated have been classified as:-

- (1) Cytolysins or immune substance.
- (2) Agglutinins.
- (3) Opsonins.
- (4) Precipitins.

Cytolysins are specific anti-bodies which produce destruction of the cell or bacterium which has acted as antigen. Under them may also be classed the proteolytic anti-bodies which bring about lysis of foreign protein molecules such as those of egg-white and milk.

The capacity of an antigen for exciting the formation of a specific cytolytic substance depends on its molecular structure rather than on its cell morphology. The injection of a cancer patient with an emulsion of carcinoma cells, for instance, does not result in the development of a cytolytic substance which is specific for Carcinoma.

The cytolsin is not destroyed by a temperature of 56° C. On being brought in contact with its specific/

specific antigen, it is fixed by it, but it is only active in the presence of complement.

The complement or alexin which is normally present in the serum, and is necessary for the phenomenon of cytolysis, is not increased in response to the introduction of Antigen. It is destroyed by a temperature of 56°C . or in other words the serum is inactivated for cytolysis. The addition of a little fresh unheated serum to the inactivated serum reactivates it, i.e. it again becomes cytolytic.

It is possible that more than one complement is present in the serum of each animal species, and that a single immune substance may be capable of uniting with several kinds of complement.

In the process of immunization, it is probable that multiple cytolysins may be developed against each particular antigen, so that the extreme complexity of the subject is apparent.

Agglutinins are probably the most widely known of the specific anti-bodies, as they have been employed, since they were described by Widal and Grunbaum in 1896, in the diagnosis of various infectious diseases such as the Enteric group, Dysenteries/

dysenteries, and Mediterranean Fever. They are frequently developed along with cytolymins, and like them they may be fixed by contact with their antigen. Bordet and other have shown that agglutination occurs as the result of a complex formed by agglutinin and antigen. They act independently of complement and are only destroyed by a temperature of 70° - 78° C.

Opsonins prepare their antigenic bacteria for phagocytosis. They were described by Wright and Douglas in 1904.

Praecipitins are highly specific antibodies which are found in the serum of immunized animals. They interact with antigen and lead to the formation of a precipitate, if a drop of immune serum is added to a dilute solution of its specific antigen.

The reaction is extremely delicate and can be employed for the detection of the specific antigen whether it be blood serum, egg-white, milk, or vegetable protein, bacterial or otherwise. The specific precipitates have the important power of fixing/

fixing and removing complement from solution. This is an important point to bear in mind in relation to anaphylactic shock in which condition complement disappears from the serum. It also produces a serious complication in the performance of the Wasserman test.

The various antibodies which are formed in the artificial production of immunity gradually disappear from the serum after a longer or shorter period if the injection of antigen is suspended.

The degree of immunity cannot be gauged by the amount of Agglutinins which are found in the serum in vitro.

The foregoing remarks refer to immunity which has been artificially induced, and also to that which arises under natural conditions as the result of infection and other natural processes. In addition there is the natural immunity to disease and to invasion by other non-bacterial foreign proteins, which exists in varying degree for various proteins in different individuals, families, and species, varying in each individual with age, nutrition, temperature, and many other conditions.

In some animals an almost absolute immunity for one disease coexists with a high degree of susceptibility/

susceptibility for another. For example rats and mice are almost immune to Diphtheria, but they are readily killed by Tetanus.

No general law can be formulated as to the conditions which constitute a natural immunity to any specific Antigen.

Tanner Hewlett ascribes it to three factors.

- (1) High phagocytic power aided by bacteriolytic properties of the serum.
- (2) The toxin cannot become anchored to the cells because the cell molecules do not possess receptor groups which have a special affinity for the haptophore groups of the toxin molecule.
- (3) The toxin molecule may be fixed by the cells, but has no toxic effect upon them.

He thinks that acquired immunity may be attributed to the receptor groups, which have an affinity for the haptophore group of the toxin molecule, having been used up.

Passive immunity against a specific antigen can be conferred on a susceptible animal by injecting it with the blood-serum of another animal that has been immunized to that antigen.

It is also conferred on the child by its mother.

- (a) through the placental circulation.
- (b) through her milk.

Immunity/

Immunity may be localised to certain tissues of the body. e.g. the mouth and rectum have a specially high resistance to pyogenic bacteria, and Besredka¹⁹ believes that immunity to the Enteric group resides entirely in the mucosa of the Intestine.

If we take a horizontal line to indicate normal immunity to the toxic effects of a specific antigen when introduced into the tissues, we may draw on the upper side of it parallel lines indicating higher and higher degrees of immunity and below it a series of similar lines indicating diminishing degrees of immunity or in other words increasing degrees of susceptibility.

Pasteur's researches revealed that the immunity of an animal to a particular antigen can be greatly increased by repeated injections of sub-toxic doses of the antigen. This was in agreement with the clinical observation that many diseases such as Small-pox and Measles confer a high degree of immunity on their victims against a subsequent attack.

This was followed by, the immunizing of horses against Diphtheria, Tetanus, and other toxins, and the employment of their highly immunized serum in producing passive/

19. *Anaphylaxis & Anti-anaphylaxis*. translated by Ployne.

passive immunity in susceptible subjects who were exposed to the toxic action of the specific antigen.

While pursuing these investigations, Behring observed the phenomenon of what he called "Hyper-susceptibility" in dogs, but he did not then realize its importance or meaning, and it was Chas. Richet²⁰ who in 1902 discovered the fact that in endeavouring to produce a heightened artificial immunity by the injection of foreign protein, one might instead, produce an extreme degree of specific susceptibility. When he made this discovery, he was endeavouring to immunize a dog to "Congestin", a protein extract of the tentacles of the sea anemone. The dog had suffered no ill effects from the first injection, and twenty two days^{later} was given a second immunizing injection of the same dose as on the first occasion. Within a few seconds the dog was seized with collapse, vomiting, blood-tinged diarrhoea, & dyspnoea, and died thirty five minutes after injection.

As this paradoxical result, was the very reverse of the prophylaxis that he had expected to establish, Richet termed it "anaphylaxis". His epoch-making observation was followed by an enormous amount of work/

²⁰. Richet, "Anaphylaxis". Translated by Murray Bligh

work by investigators in all countries with the object of explaining the meaning of the phenomenon, the circumstances under which it occurs, and its mechanism.

From a bewildering welter of speculation one may endeavour to extract a few of the proved facts.

- (1) Under normal conditions foreign protein substances do not enter the body or circulate in its fluids.
- (2) Experimentally they have been introduced by subcutaneous and intravenous injection, and the study of Anaphylaxis has been founded and built up mainly on these experimental conditions, which are a violation of the natural defences of the body.
- (3) The introduction of a single sub-toxic dose of an antigen, has in the normal animal, no outward and visible untoward effects, but after a latent or incubation period of twelve days or more, the tissues of the animal may have developed a condition of undue sensitiveness or diminished immunity to the antigen, so that once this condition is established, a second injection of antigen, even in smaller amount than the first dose, induces with startling suddenness a condition of anaphylactic shock.

This anaphylactic reaction is highly specific. The first injection of antigen is called the sensitizing or exciting dose. The second injection is called the toxogenic or reacting dose.

Within certain limits the incubation period of sensitization varies directly with the amount of the sensitizing dose. The larger the dose of antigen, the/

the longer is the incubation period, even up to forty²¹ days.

The manifestations of Anaphylaxis may be local as well as general.

The local manifestation consists of a very painful, indurated swelling at the site of the toxogenic injection, which may even undergo aseptic necrosis - the so-called phenomenon of Arthus.²²

The systemic manifestations of Anaphylaxis vary in quality and degree in different species of animals.

The Guinea-pig, Horse, and Goat, are very readily sensitized. The Rabbit, Dog, and Man are less susceptible, and the Mouse is almost completely insusceptible.

The readiness with which sensitization and anaphylaxis can be induced, varies with the mode of injection of Antigen. These are in order of certainty (1) Intracerebral and intravenous; (2) Intramuscular; (3) Subcutaneous, intra-peritoneal, or intra-pleural;²³ (4) intra-theal.

²³ Dale has shown that in Anaphylactic animals there are two outstanding features.

- (1) Depression of capillary tone with capillary engorgement, oedema, and extravasation, the result of injury to the capillary endothelium.
- (2) Increased tonus of plain muscle, throughout the body - bronchial, intestinal, uterine and arterial.

Both/

²¹ Tanner Hewlett, *Manual of Bacteriology*. 7th Ed.

²² Arthus, *Compt. rend. du Soc. Biol.* 1903. LV. p. 917.

²³ Hester Lectures, 1919. *Bull. Johns Hopkins Hosp.* 1920. XXXI

Both these features are prominent in varying degree in the Guinea-pig, Rabbit, Cat and Dog.

The Anaphylactic Guinea-pig dies of Asphyxia from spasm of the plain muscle of the bronchioles, which, owing to the peculiar anatomical arrangement of the Guinea-pig's bronchial mucosa, produces complete obstruction of the respiratory air-way. The rabbit dies from acute over-distension of the right heart, secondary to spasm of the branches of the pulmonary arteries. In the dog there is capillary engorgement from loss of capillary tone. Capillary engorgement of the liver is a very marked feature. As a result of this capillary engorgement, there is depletion of the arteries and symptoms of collapse. Spasm of the plain muscle of the bronchioles and other viscera does occur but is of secondary importance.

Anaphylactic phenomena in Man resemble more closely those which occur in the dog than those which occur in the Guinea-pig.

The phenomena of anaphylaxis are the same whatever protein is employed as antigen. They are just as likely to follow a small sensitizing dose as a larger one/

one and their intensity bears no relation to the size of the sensitizing dose. A very small dose of Antigen may be sufficient to sensitize an animal, e.g. an ordinary guinea-pig can be sensitized by only 0.000,001 gramme of protein.

A striking parallel to the phenomenon of the production of passive immunity is found in the fact that sensitization to a specific antigen can be conferred on an insusceptible subject by the injection of the serum of a sensitized animal.

Bruck²⁴ injected two guinea-pigs with the serum of a man who was sensitized to Pork. Twenty four hours later he gave them an intra-peritoneal injection of hog serum. Both developed typical Anaphylaxis. Four controls remained well. Now that blood transfusion has become an established practice there is danger that the recipient may become passively sensitized by the donor's blood. Ramirez²⁵ has reported a case of a man who developed violent asthma from the proximity of a horse a fortnight after being transfused with 600 cc. of blood from a donor who was a horse-asthmatic. Like passive immunity, passive sensitization/

24. *Arch. f. Dermat. u Syphil.* 1909 *xcvi*. 241.

25. *Trans. Amer. Med. Assoc.* Sept. 27. 1919.

sensitization dies out after a comparatively short interval. If an animal recovers from anaphylactic shock, it is some time - ten or twelve days at least - before it recovers its specific sensitization. During this period of "Anergy" as it is called in contradistinction to "Allergy" or sensitization, large doses of antigen can be injected with impunity and the animal permanently immunized.

Anaphylactic shock does not occur if the sensitized animal be under a general anaesthetic or deeply under the influence of chloral hydrate at the time of the second injection of antigen. It can also be prevented by a previous injection of atropine; by eliminating the liver from the circulation; by injecting the second dose very slowly and intermittently; or by the addition of a certain quantity of Sodium Hyposulphite or Sodium Chloride to the second dose of Antigen.

Injections of Peptone in sufficient dosage produce all the characteristic reactions of Anaphylactic shock without a previous sensitizing dose. The reaction varies characteristicallyⁱⁿ different species.

²⁶ Weill showed that if a normal liver be perfused with peptone, it quickly presents the same swelling and capillary congestion as does the liver of a sensitized animal after an injection of Antigen.

Still/

Still more interesting is the fact that Histamine²⁷, a non-protein substance, is also capable of producing all the phenomena of Anaphylaxis in an unsensitized animal. Histamine is an amine which can be derived by the decarboxylation of the Amino— Acid Histidine which is a derivative of Ergot. Berthelot and Bertrand²⁸ have isolated organisms from the intestine which have the power of forming Histamine, and Eustis²⁹ has found Histamine in the stools of asthmatics. It is present in commercial peptones and proteoses and also in commercial extract of Pituitary.²⁸

Again it has been found that shock closely resembling Anaphylaxis results from the injection of various nitrogen-free substances such as Pectin, pararabin, and silicic acid. It is probable however that these substances produce their effect by intravascular clotting, and their action is not related in any way to the Antigemic substances which produce a true anaphylaxis.

The condition in man, which is most closely analogous to the experimental condition of anaphylaxis in animals, is Serum Sickness, which occurs in the sero-therapeutics of various infectious diseases.

Goodall²⁶ in an analysis of 200 cases of reinjection of Diphtheria antitoxin after an interval varying from two/

27. Dale, Hunter Lectures, 1919.

28. Quoted by Coker, B.M.A. meeting, B.M.J. Aug 13, 1921 p. 236.

29. British Jour. of Childs. Dis. Oct. 1912.

two weeks to thirteen years, found that Serum Sickness occurred in 56% as compared with 33% after primary injections. The type of sickness was generally of greater severity in the reinjected cases than in the primary ones. This clearly shows the influence of sensitization.

C.B. Ker³⁰ describes Anaphylactic shock after a second injection of serum in a sensitized patient as follows:- "The patient is collapsed and dyspnoeic. The face is cyanosed. Oedema rapidly appears. A rash, urticarial usually, sometimes Scarletiform, appears within half an hour. The pulse is soft, small, and rapid".

From the study of Serum Sickness in the sensitized subject it is generally inferred that there are varying degrees of Anaphylactic toxæmia from slight toxæmic symptoms, e.g. Urticaria, up to severe toxic shock which culminates in death.

The phenomenon of Arthus is of common occurrence in the sensitized human subject after an injection of serum.

In individuals who are sensitized to a particular antigen, there can usually be obtained a local inflammatory reaction of the skin when a solution of the/

30. "Infectious Diseases". 2nd Ed.

the antigen is applied to an abrasion of its surface. This will be referred to in more detail at a later stage.

Technically, only subjects who have been artificially or naturally sensitized to antigen can exhibit the phenomenon of anaphylaxis in any degree. The phenomenon of natural hypersusceptibility is placed in a different category, although its manifestations on the introduction of antigen appear to be identical with those of artificial sensitization. In fact, hypersusceptibility or idiosyncrasy to any protein would appear to bear the same relation to sensitization, that is acquired by natural or artificial means, as natural unacquired immunity does to an immunity that is induced artificially or as the result of natural infection.

Both varieties can be studied and compared in the case of serum sickness, in the human subject. The disease presents practically no difference whether occurring in the previously sensitized or in the naturally hypersusceptible patient except that the former class is more numerous than the latter.

THE BIO-CHEMISTRY OF ANAPHYLAXIS.

The essential physico-chemical processes which underlie the grosser manifestations of sensitization and anaphylaxis have given rise to much investigation and a voluminous literature. The views of some of the chief workers at the subject will be briefly summarised.

- (1) Richet³¹ holds that the initial introduction of Antigen causes the elaboration in the blood or fixed cells of an antibody which he calls "Toxigen". A second introduction of antigen at the end of the latent period leads to a reaction between it and the toxigen. The antigen molecule is split, and a toxic substance called "apotoxin" is set free which produces the anaphylactic shock. The toxicity of the apotoxin is increased by combination with complement and accounts for the disappearance of that substance.
- (2) Von Pirquet and Schick³² considered that the essential process was an interaction between antigen and its specific antibody with the setting free of a product which interacted with the still-circulating remnants of antigen.
- (3)/

31. "Anaphylaxis". Translated by Murray Bligh

32. Quoted, Delapuehl & Prudden's Text book of Pathology. v. Pirquet. Archives Intern. Med. 1911. VII. 259, 323

- (3) Wolff-Eisner³³ in 1904 suggested that the first injection of antigen led to the formation by the body cells of a ferment which was capable of splitting the protein molecule into toxic radicals.
- (4) Vaughan³⁴ has strongly supported this view and has done much experimental work to prove that the toxin which produces anaphylactic shock is a split protein radical.
- (5) The discovery that the injection of an unsensitized animal with a suitable dose of peptone solution induces a state of shock, that is indistinguishable from anaphylaxis, gave rise to the view that peptones and proteoses were the toxic split - protein radical of Wolff-Eisner and Vaughan, produced by the proteolytic action of antibody on antigen, in fact that apotoxin was almost identical with Witte's peptone.³⁵ Jobling and Bronfenbrenner³⁶ stated that peptone was present in the blood of anaphylactic animals, and explained the anaphylactoid shock which follows the injection of non-nitrogenous substances like pararabin, by the suggestion that peptone/

33. *Centralblatt. f. Bakteriöl. Orig.* 1. 1904, XXXVII. 350, 366, 384.

34. "Protein split-products in relation to immunity & disease." Philadelphia. 1913.

35. Biell & Kraus. *Wien Klin. Woch.* No 11

36. *Ann. Exper. Med.* 1914-15. Various papers.

peptone-formation occurred in these cases also from autolysis of the proteins of the blood-serum. These observations and theories of Jobling and Bronfenbrenner were, however, controverted by the experiments of Van Slyke and Auer.³⁷

- (6) Dale³⁸ working with Histamine found that, while very minute doses produce a constriction of the arterioles and relaxation of the capillaries, larger doses - 1-2 mgm. per kilo of the body-weight - produce all the phenomena of Anaphylaxis. He therefore infers that anaphylaxis is due to some protein-cleavage product identical with, or closely similar to Histamine which is produced as a result of the interaction in the cells of Antigen and its specific antibody, which is probably a precipitin, this interaction producing an alteration in the state of dispersion of the protoplasmic colloids. He suggests that secondary wound shock may be due to the formation of a histamine-like substance from autolysis of the proteins of the damaged tissue.

- (7) Gay and Southard³⁹ hold that Antigen consists of two elements, one toxic called anaphylactin, which is/

37. *Jour. Exper. Med.* 1915, XVIII, p. 210.

38. *Hunter Lectures*, 1919. *Bull. Johns Hopkins Hosp.* 1920 XXXI 257, 310, 373.

39. *Jour. Med. Res.* 1907, N.S. XI, 143.

is quickly eliminated, the other non-toxic, but capable of sensitizing the tissue cells to reintroduction of anaphylactin.

- (8) Besredka⁴⁰ also takes the view that Antigen consists of two elements. One is a thermos-
table, antigenic substance which he calls sensibilisogen which is fixed by the cells of the central nervous system and gives rise to the formation in them of a specific antibody called sensibilisin; the other is a thermo-
labile substance called the anti-sensibilisin, which has a violent affinity for sensibilisin. On the introduction of the reacting dose of antigen, a violent reaction is supposed to take place between its anti-sensibilisin element and the sensibilisin in the nerve cells. Anaphylactic shock is the result, unless the nerve cells have been rendered insensitive by an anaesthetic.
- (9) Novy⁴¹ found that when normal serum is digested with Witte's Peptone, a toxic substance results which he believed to be identical with that which occurs in the body cells and fluids during anaphylactic/

40. *Anaphylaxis et Anti-anaphylaxis*. Paris 1917. Translated by Hargreaves.

41. *Jour. Infect. Dis.* May & June 1917.

anaphylactic shock, as injection of it was followed by a similar explosive effect. He considers the antigen to be merely an inducing agent and to be entirely recoverable after the antigen-antibody product has induced the production of the anaphylactic poison by the blood and tissue cells.

- (10) Friedberger⁴² found that the interaction of complement with antigen produces a toxic substance, which he calls anaphylotoxin, and that this, when injected into a sensitized animal, produces all the phenomena of anaphylactic shock. He also found that if the specific antibody was present along with complement, anaphylotoxin was produced more rapidly and in larger amount. This view would also explain the disappearance of complement in anaphylaxis.

- (11) Doerr and Russ⁴³ regarded anaphylactic shock as an intracellular precipitin reaction.

- (12) Weil⁴⁴ also regarded it as due to an intracellular reaction between antigen and its specific antibody, a precipitin, which is anchored in the cells/

42. Quoted by James Hewlett. *Manual of Bacteriology* 7.th Ed.

43. *Ztschr. f. Immunitätsforschung*. 1911. Orig. 1409 III. 131.

44. *Jour. Immunol.* 1917. II. 429.

cells. He thought that the only difference between an immunized and a sensitized animal, lies in the fact that in the former there is an abundance of antibodies in the blood-serum, which fix the antigen and protect the cell; whereas in the latter the antibodies have been mostly anchored in the cells and are present in the blood serum in insufficient quantity to protect the cell from the toxic effect of the antigen and its split products.

- (13) ⁴⁵Kopaczewski, working at the Pasteur Institute in Paris, found that toxic shock, closely resembling anaphylaxis, could be induced by contact of serum with Pectin - a nitrogen free colloidal substance.

Bordet and Schmidt obtained a similar result with pararabin and starch respectively both being nitrogen-free substances.

Examination of the toxic serum with the ultra-microscope revealed an agglutination of the ultimate molecular mass of its protoplasm. This he considers to/

⁴⁵. *Annales de Médecine*. Paris. 1920. 7. N°5. p.361.

to be a specific phenomenon which occurs only in the toxic sera. Only colloidal substances in the gel state, of a certain structure, and having a pronounced electro-negative charge are capable of this toxic action.

Kopakzewski regards anaphylaxis as due to a colloidal agglutination, which by obstructing the capillaries, suspends vital function.

There was formerly a great conflict of opinion between the so-called Humoural and Cellular theories of anaphylaxis. The former held that the formation of the apotoxin took place entirely in the blood, the latter that the interaction of antigen and antibody was confined to the tissue cells.

The latter view has now gained the ascendancy, for although the phenomenon of passive sensitization shows that the antibodies which generate the toxin from antigen, are present in the blood serum, it has nevertheless been shown by Rumpf⁴⁶ that entire replacement of the blood of a sensitized animal with normal blood does not prevent anaphylaxis, and by Von Fenyvessy and Freund⁴⁷ that the presence of antibodies in the circulation is not necessary for the production of anaphylaxis. Dale⁴⁸ found that if the specific antigen/

⁴⁶. Quoted by Delapfield & Prudden.

⁴⁷. *Ztsch. f. Immunitatop.* 22: 199. 1914.

⁴⁸. *Horten Lectures*. 1919

antigen was added to the solution which was used to perfuse the excised uterus of a sensitized rabbit, the uterus was at once thrown into a state of tonus. This, along with the complementary fact that perfusion of the liver of a sensitized animal with the specific antigen induces a capillary congestion of the organ, that is typical of anaphylaxis, indicates that the antigen-antibody reaction which results in the formation of apotoxin is intracellular.

To sum up;-

- (1) Anaphylaxis is caused by a toxin which is formed as the result of an intracellular reaction between antigen and its specific antibody.
- (2) The similarity in action of apotoxin, peptone, and histamine is strongly suggestive of apotoxin being a derivative of proteolytic action and closely allied to histamine.
- (3) It is uncertain whether Apotoxin is formed as the result of a simple interaction between antigen and antibody, or is indirectly produced from the cell proteins, as a result of an alteration in the state of dispersion of the protoplasmic colloids/

colloids of the cell, which is set up by the antigen-antibody reaction.

- (4) The central nervous system is intimately concerned in the production of the phenomenon, but its exact relation to it has not been determined.
-

CHANGES IN THE CIRCULATORY SYSTEM AND BLOOD.

Widal and Abrami⁴⁹ have drawn attention to what they call a "Crise Hémoclasique" which occurs in anaphylactic shock, in protein shock, and also in asthma and various allied conditions in man. There is a fall in arterial blood-pressure, a leucopenia, hyper-viscosity, and decreased coagulability of the blood.

Eosinophilia is also a very constant and important feature in anaphylactic shock. It is evident in the local exudate of the Arthus phenomenon as well as in the peripheral circulation. Schwenker and Schlecht⁵⁰ stated that Eosinophilia occurs in anaphylaxis from inhalation and ingestion of protein, as well as in the ordinary experimental anaphylaxis. They noted that if a guinea-pig recovered from anaphylactic shock, it showed marked eosinophilia, and thought that it indicated a favourable reaction to the toxin. They also called attention to the Eosinophilia in the nasal and bronchial secretions of hay fever and asthma patients.

Herrick, /

49. *Presse Médicale* 1914. p. 525

50. *Ztschr. f. Klin. Med.* LXXVI. p. 77

⁵¹
Herrick, working with guinea-pigs, and using an aqueous extract of Asearis as his antigen, found that an intra-peritoneal injection of the extract produced an eosinophilia of the peripheral blood after a previous sensitizing dose.

The eosinophilia was in response to a protein in the extract.

It did not occur so long as an animal was immune to the extract.

It commenced after the anaphylactic period and disappeared in 24 - 72 hours.

⁵²
Rackemann states that foreign protein is an eosinotactic substance.

⁵³
Weinberg and Sequin state that Eosinophilia appears one to three days after the toxigenic dose of antigen, owing to its direct irritation of the haemo-poietic system.

⁵⁴
Cowie and Colhoun hold that a blood-crisis without Eosinophilia is not an anaphylactic condition.

51. *Arch. Internat. Med.* Feb. 1913.

52. *do.* Oct. 1918

53. *Compt. Rend. Soc. de Biolog.* 76

54. *Arch. Internat. Med.* Jan. 1919.

LV. VARIOUS MORBID STATES IN MAN AND THEIR
RELATION TO ANAPHYLAXIS.

Scientific opinion as to the correlation of various morbid states in man with the experimental condition of anaphylactic shock in animals is still in a state of uncertainty and flux.

The great bulk of opinion is however in favour of the postulate that serum sickness, hay fever, asthma, urticaria, and various cutaneous and other disorders are due to sensitization of the body to foreign protein, and are closely related to the anaphylactic phenomena that occur in animals. This opinion is based on the following observations.

In animal experiments typical sensitization and anaphylaxis can be produced by injections of the proteins of egg and milk, and many other animal and vegetable proteins.

In human beings who have been born with or acquired ^{an} "idiosyncrasy" for these same protein substances,

(1) they usually produce a specific cutaneous reaction.

(2)/

- (2) Their ingestion or inhalation is followed by definite gastro-intestinal and cutaneous disorders or by asthma.
- (3) The intradermal test has been found to be dangerous in these cases owing to their liability to develop definite symptoms of shock.
- (4) Desensitization for the offending substance can be accomplished by various methods, specific and non-specific, that are effectual in experimental anaphylaxis.
- (5) Eosinophilia both in local exudates and in the periplural circulation is a constant feature in experimental anaphylaxis and is commonly present in asthma, hay fever, urticaria and many other conditions that have been correlated with it.
- (6) A "crise hémoclasique is often present"

A very definite link between anaphylaxis in animals and asthma and allied disorders in man would seem to be provided by the phenomena associated with the subcutaneous injection of serum in man. As already mentioned, serum sickness occurs with greater frequency and severity in those who have had a previous/

previous dose within the period appropriate to sensitization. The asthmatic and particularly the horse-asthmatic is notoriously a dangerous subject for injection of horse serum, even in minute doses.

Boughton⁵⁵ reported the case of a horse-asthmatic who was given one minim of horse serum intravenously as a desensitizing^{si} dose. Within two minutes an attack of asthma came on, collapse supervened, and death occurred in forty minutes.

The local phenomenon of Arthusis of very common occurrence and differs in no way from that which occurs in sensitized animals.

The urticarial and erythematous eruptions, the collapse and dyspnoea, and the occasional fatal issue all bear a close resemblance to the picture of anaphylaxis in animals and like it, they can be prevented or relieved by similar methods of desensitization, as well as by anaesthetics and other drugs.

A specific cutaneous reaction to horse-serum is usually obtained.

On the other hand many prominent investigators deny that there is any true analogy between experimental anaphylaxis and these affections. One of their strongest/

55. Jour. Amer. Med. Assoc. 1920. p. 1912

strongest arguments is that in animals anaphylaxis appears almost before the introduction of antigen is complete, whereas the phenomena that are attributed to anaphylaxis in man, are never so rapid in onset, but require minutes, hours, or even days, instead of a few seconds for their appearance.

⁵⁶
Coca considers that if anaphylaxis does occur in man, it does so very rarely, and that there is no positive evidence that it does occur at all.

⁵⁷
Jousset, writing on the "Myth of Anaphylaxis", protests that "every obscure phenomenon in pathology, every instance of medicinal intolerance, and every sort of alimentary intoxication have been one after another classified under this head. At the present time for a pathological event to be described as due to Anaphylaxy, it will suffice that it be inexplicable or simply disconcerting".

He states that "In sero-therapy there is no such thing as Anaphylaxis", and points out that the most violent toxic shock, following an injection of serum in man, is not comparable to the anaphylaxis of Richet.

He however, issues a warning against the intravenous injection of serum and admits the seriousness of/

- Imm. Immunol. 28 1910*
56. *Hypersensitiveness, Anaphylaxis, & Allergy*. New York, p. 363
57. *The Medical Press* 24.9.19 p. 250.

of the Arthus phenomenon, so that his objection to the use of the term Anaphylaxis is one rather of degree than of quality, as the phenomena of anaphylaxis admittedly vary greatly in different species of animals.

Auer⁵⁸ while admitting specific hyper-sensitiveness to Proteins, as seen in the serum sickness, hay fever, asthma, eczema, and many other conditions which he considers to have much in common with hyper-sensitiveness to drugs, states that these manifestations do not correspond in many essential respects with true Anaphylaxis, though presenting many points of similarity and that it is now agreed by all that these manifestations, and more especially the drug reactions, are not even related to anaphylaxis.

Between these extreme views we have those who continue to halt between two opinions until more conclusive evidence shall be forthcoming. Wells⁵⁹ writes that "The evidence of the identity of these indications of hypersensitiveness to true anaphylaxis is so contradictory as to defy positive conclusions".

Freeman,⁶⁰ while admitting a specific hypersensitiveness in hay fever, asthma, and allied affections of the skin and other systems, classes them all under the/

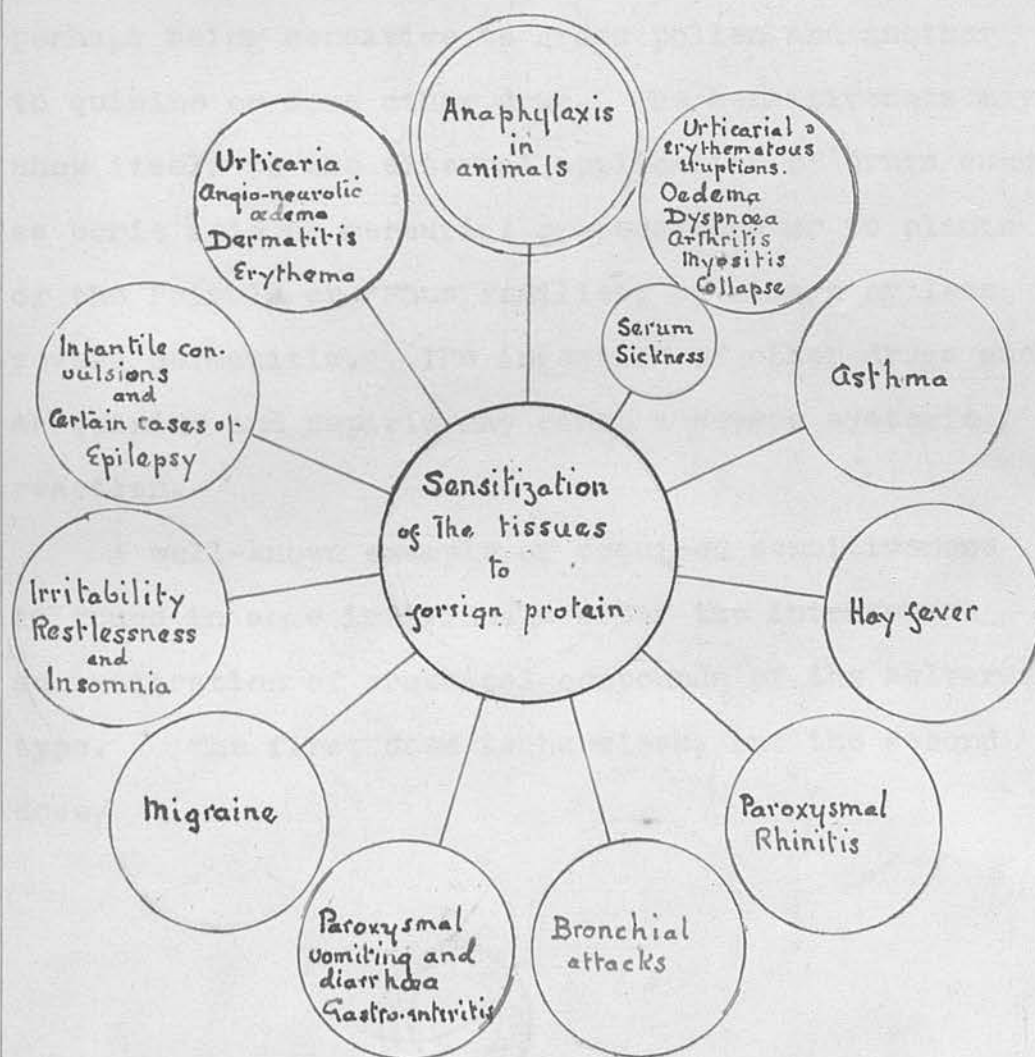
58. Jour. Exper. Med. 32 : 247 . Oct. 1920 .

59. "The present status of the problems of Anaphylaxis"
-Physiological Reviews 1 : 44 . Jan. 1921

60. Lancet. July 31. 1920. p. 229 .

the group name of "Toxic Idiopathies". Whichever view is academically correct, the outstanding fact remains that the study of anaphylaxis in animals provided the key to the elucidation of asthma, hay fever, and many other obscure conditions in man, and that specific sensitization of the tissues to foreign protein is the basic fact in both sets of conditions.

This may be illustrated by a rough diagram.



IDIOSYNCRASY AND SENSITIZATION TO DRUGS AND PLANTS.

It may be well at this stage to refer briefly to the question of hypersusceptibility to various drugs and plants.

As in the case of hypersensitiveness to Proteins this may be natural or acquired, and it is not uncommon for it to coexist with one or other protein sensitization in the same individual or family, one member perhaps being sensitive to grass pollen and another to quinine or some other drug. The sensitiveness may show itself to the external application of drugs such as boric acid or mercurial preparations or to plants of the Primula or Rhus families, by a more or less severe dermatitis. The ingestion of other drugs such as quinine and aspirin may cause a severe systemic reaction.

A well-known example of acquired sensitiveness is found in some individuals after the intravenous administration of arsenical compounds of the salvarsan type. The first dose is harmless, but the second dose/



dose may be followed by various grades of toxaemia from a mild urticarial or erythematous eruption, to severe toxic shock. The repeated local application of certain drugs such as strychnine, morphine, procaine and formaldehyde induces in certain people extreme hypersensitiveness of the exposed parts so that the slightest re-exposure will result in an acute dermatitis. Sensitiveness to certain plants may likewise be acquired by repeated application of the juice or of sawdust.

Until recently the eruptions and other toxic effects of drugs and plants were explained in various ways as:-

- (1) An idiosyncrasy of the patient.
- (2) A cumulative action of the drug, it being supposed that for various reasons elimination did not keep pace with absorption and the drug was stored up in the tissues until sufficient had accumulated to produce a toxic effect.
- (3) An elective affinity of the cutaneous glands for certain drugs.
- (4) Behrend⁶¹ supposed that the chemical action of the drug on the body tissues and fluids led to the/

61. Quoted by Malcolm Morris, "Diseases of the Skin", 6th Ed. p. 511

the generation of a toxic substance which was probably chemical in nature.

- (5) Malcolm Morris⁶¹ believes that most drug eruptions are the result of an angio-neurotic process excited by the direct irritation by the of drug-nerve endings in case of its local application, and of nerve centres in case of its ingestion, the angio-neurotic process being predisposed to by an underlying idiosyncrasy or, what is the same thing, an abnormal excitability of the nervous system.

- (6) Now many have boldly applied the theory of anaphylaxis to explain the toxaemia.

Bruck⁶² passively sensitized a guinea-pig with the serum of a man who was hypersusceptible to antipyrin and then induced anaphalactoid shock by an injection of antipyrin.

pork

pigs serum

Klausner⁶³ got similar results in rabbits with the serum of a patient who had an idiosyncrasy for iodoform and iodides.

Coke⁶⁴ in speaking of sensitiveness to aspirin and other drugs refers to the same phenomenon of/

61. *Diseases of the Skin*, 6th Edn., p. 511.

62. *Arch. f. Dermat. u. Syphilol.*, 1909, XCVI, p. 241

63. *Ibid.*, 1909, XCVIII, p. 323.

64. *B.M.J.*, Mar. 12, 1921, p. 374.

of passive sensitization of animals with the serum of drug sensitive subjects.

This phenomenon of passive sensitization, the "Herxheimer reaction", which is more liable to follow a second than a primary injection of Salvarsan, and the character of the drug eruptions give some grounds for linking them up with the conditions due to protein sensitization though the exact nature of the connecting link, if indeed it exists, is not understood.

It has been suggested that the drug so acts on proteins of the body as to convert them into what are virtually foreign proteins, which produce the sensitization and anaphylaxis.

An interesting point in connection with this is that desensitization to drugs has been successfully practised by various methods that are appropriate to protein sensitization.

Auto-sero-therapy has been successfully employed in Urticaria, Angio-neurotic oedema, and hay fever and is also said to be of value in rendering hypersusceptible patients tolerant of salvarsan.⁶⁵

Laroche, Richet and Saint Girons⁶⁶ state that hyper/

65. Nicolas, Galt, & Dupasquier, *Ann. de Derm. & Syphil.* N°3, 1921

66. "Alimentary Anaphylaxis". *Extracted from Am. Med. Ass.* 14:8:1920.

hypersensitiveness to quinine can be overcome

by giving one Mgm. of quinine and 0.5 gm.

Soda Bicarb one hour before the ordinary therapeutic dose.

V. ON CERTAIN LOCAL TISSUE REACTIONS TO FOREIGN
PROTEIN IN THE SENSITIZED HUMAN SUBJECT.

Von Pirquet introduced the word allergy to indicate the altered reactivity of the sensitized body tissues to a reintroduction of specific infective material.

A practical application of this altered reactivity of the tissues has been made in the Calmette and Von Pirquet tests for tuberculous infection in man, the Tuberculin test for tuberculosis in cattle, the Mallein test for Glanders in horses, the Trichophytin test for Ringworm in children, and Casoni's test for hydatid disease. These tests depend on the fact that when the specific allergin is brought into contact with the sensitized tissues

- (1) A local inflammatory reaction is set up.
- (2) If absorption takes place a systemic reaction occurs, which is indicated by malaise, rise of temperature and other symptoms.

The term Allergy has now been extended by many to include sensitization to all antigenic substances, bacterial/

bacterial and otherwise, and also sensitization to non-protein chemical substances such as salvarsan and mercury.

Just as in a patient who is sensitized to the tubercle bacillus and its toxins, a drop of dilute tuberculin solution in the conjunctiva or on an abrasion of the skin will set up respectively a violent conjunctivitis (Calmette's reaction) or a local inflammatory reaction in the skin (Von Pirquet's reaction), so in a hay fever patient a solution of grass pollen extract in the conjunctiva causes conjunctivitis; applied to an abrasion of the cuticle it produces an inflammatory reaction indicated by a wheal surrounded by hyperaemia; if swallowed it sets up gastro-enteritis; and if introduced into the rectum it causes proctitis, showing that all the body tissues are sensitized to the pollen allergin.

If the pollen protein gains entrance to the general circulation whether by absorption from the respiratory tract, by ingestion, by absorption from a large cutaneous abrasion, or by hypodermic injection, constitutional effects *** also result, viz. lassitude, depression, irritability, urticaria or oedema, and asthma.

Similar/

Similar reactions may be set up in patients who are sensitized to food and other proteins on introduction of the specific allergin. For example, a person who is sensitized to egg-white may, on swallowing a spoonful of egg, immediately suffer burning pain and oedematous swelling of the lips and tongue; vomiting, collapse and urticaria. The application of egg-protein to a cutaneous abrasion will give rise to a marked local reaction and the subcutaneous injection of egg albumen may give rise not only to a local reaction but to toxic shock.

Auer⁶⁷ has drawn attention to a phenomenon in the anaphylactic animal that may have a practical bearing in explaining some of the clinical phenomena of sensitization in man, including the skin reaction.

He found that in sensitized animals a healthy operation wound would become inflamed and indurated if the animal were rendered anaphylactic. Similarly an ordinary rubefacient like Xylol, applied to the ears of a sensitized animal produced hyperaemia only, but if the animal were rendered anaphylactic, instead of hyperaemia there was severe inflammation, which might go on to actual gangrene. This is due to the antigen which/

67. *Jour. Exper. Med.* 32: 427 (Oct.) 1920

which is poured out into the tissues with the exudation from the dilated capillaries setting up a local reaction with the sensitized tissues, just as if it had been injected into them. This provides a satisfactory explanation for the specific skin reaction in sensitized individuals.

For the detection of a specific antigen in a case of suspected sensitization, a cutaneous reaction is obviously a convenient test if it can be proved to be specific and reliable.

During the past few years a great deal of work has been done, especially in America, on specific skin reactions to protein substances in cases of asthma, skin affections, and other conditions that have been thought to be linked up with the condition of anaphylaxis. Two methods have been employed, the intradermal and the cutaneous.

The intradermal test has been employed by Strickler, Goldberg, Chandler-Walker and others.

It consists in the injection into the skin of a minute quantity, - about 0.1 cc., - of a dilute solution of the suspected protein. A positive reaction is indicated by the formation at the site of injection/

injection of a distinct papule with erythema and local tenderness, which lasts from a few hours up to forty eight hours or longer.

It is not a method that is ever likely to attain popularity or that can be recommended for general use. The objections to it are:-

- (1) The injection is unpleasant, especially when many proteins have to be tested for, and reactions are painful.
- (2) In a young or nervous patient it is difficult to perform.
- (3) An inflammatory reaction cannot be accepted as specific.
- (4) In highly sensitive subjects it is liable to cause severe toxic symptoms.

Gerstenberger and Davis⁶⁸ recently reported the case of a child aged one year which suffered from "Eczema and Bronchial Wheezing". As the cutaneous test to egg was negative, they applied the intradermal method. While injecting egg-white and egg-yolk, marked cyanosis and dyspnoea developed and was relieved by adrenalin. Next day the child had urticaria. There/

68. Jour. Amer. Med. Assoc. 76:721. Mar. 12, 1921

There was a wheal at the site of injection. On the third day intradermal tests with other proteins were made without untoward effects or local reaction. Three days later egg-yolk allergin was again injected intradermically and within a few minutes the child was again cyanosed, and dyspnoeic, and was only saved by an injection of adrenalin. The local reaction was again positive.

The cutaneous test is the one generally employed, and is free from the disadvantages of the intradermal method. The tests are most conveniently applied to the flexor aspect of the upper arm and forearm, but if for any reason, such as a dermatitis, this region is not suitable, healthy areas of skin on the thighs, abdomen, or chest may be employed.

A point of importance is to avoid applying tests in the flexure of the elbow, as the normal reaction to trauma is usually more marked there than in other parts of the arm. For the tests crude food substances such as egg-white, beef, or potato may be used, but it is more convenient and more scientifically accurate/

accurate, to use the special sets of test proteins which are prepared by certain chemical firms. I have employed those prepared by the Arlington Chemical Co., of Yonkers, U.S.A., and they are believed to be pure and reliable preparations.

Decinormal solution of Sodium Hydrate is used as a solvent for the proteins.

The technique which I employ is as follows. Having ascertained from the patient's history what food he is accustomed to eat, and any special article of diet or circumstance of environment that may be suspected of causing his symptoms, a list of test-proteins with a control at the beginning and end of the list is made out for either arm. The phials of protein are laid out in corresponding order along with a scarifier or burr, some fine glass rods for applying the protein, and a hypodermic syringe filled with N/10 Sodium Hydrate solution. The syringe makes a convenient dropper.

The patient's skin is cleansed with absolute alcohol and dried.

The abrasions are then made either with a small dental burr, which abrades the cuticle without drawing blood/

blood, or by making a scratch one eighth of an inch long through the horny layer of the epidermis just short of drawing blood. A fine sharp-pointed knife is used for this purpose so as to avoid trauma as much as possible. I have used both methods and on the whole I think that the incision is to be preferred as it causes less traumatic reaction than the burr.

The number of abrasions corresponds to the number of test proteins and controls on the list. They should be at least $1\frac{1}{2}$ inch apart.

On to each abrasion a drop of N/10 Sodium Hydrate is dropped from the syringe. The phials are opened in turn, and a little of the protein extracted on the end of a glass rod and stirred into its special drop of sodium hydrate till dissolved.

An absolutely clean rod must be used for each test or if preferred, a wooden spatula may be fashioned from a match and thrown away after use. On the controls only Sodium Hydrate is put.

A positive reaction will show within ten to thirty minutes as a raised wheal surrounded by a zone of hyperaemia.

⁶⁹Freeman states that the reaction is sometimes delayed even as long as fourteen hours or more to both/

⁶⁹ *Lancet*, July 31, 1920, p. 234.

both food and bacterial proteins. My Case No.11 is possibly an example of this. It must be remembered that in the normal person, the abrasion produces a small wheal surrounded by more or less hyperaemia and, as above mentioned, that the reaction in the elbow bend is usually larger than those in other situations. The amount of reaction to the abrasion varies greatly in different individuals. In those who show the phenomenon of dermatography it may be very great.

In all cases the test reactions must be judged by the standard of the controls. Various standards are adopted.

Chandler Walker⁷⁰ advises that no wheal less than 0.5 cc. in minimal diameter should be accepted as a positive reaction.

Coke⁷¹ accepts $\frac{1}{4}$ inch diameter as a positive reaction.

Highman and Michael⁷² recommend that a test wheal of about the same size as the control wheal should be considered negative; half as large again: + ; twice as large ++ and so on. Foote⁷³ states that a + reaction should be three times larger than the control.

The variation in these standards shows how strongly the personal factor enters into the interpretation of the tests. There is undoubtedly a great temptation to adopt too low a standard, as the carrying/

70. Boston Med. & Surg. Jour. Aug.29. 1918.

71. B.M.J. Mar.12. 1921.

72. Arch. of Derm. & Syphil. Nov.1920.

73. International Clinics IV. Series 30. p.212.

carrying out of the tests involves much time and care, the proteins are expensive, and there is a natural desire to prove that one's labour is not in vain. On the other hand insistence on too high a standard may cause one to disregard what may be a clue to diagnosis.

My own standard is a modification of Highman and Michael's. A test wheal of the same size as the control is considered to be negative and recorded as -

Half as large again, - doubtfully positive (+-)

Twice as large, - positive (+)

Three time as large: strongly positive (++)

The value of the cutaneous test depends upon its specificity, and there is a very large amount of evidence which has been collected over a considerable period by many different investigators, that reactions are in the main specific. For instance a positive reaction to egg-white in a child is strong presumptive evidence that that child's dietary has included egg, even should the parents deny it. Foot⁷⁴ records three such cases of which one may be cited.

An artificially fed infant, eight months old, was seen for eczema, from which it had suffered since it was taken off the breast five months previously. It gave a +++ cutaneous reaction to egg. The parents denied/

74. Foote. International Clinics. Vol.IV. Series 30 p.212.

denied that it had been given egg, but enquiry proved that it was being given "cookies" which were glazed with egg.

Freeman⁷⁵ states in regard to hay fever that "the specificity of the ophthalmo-and cutaneo-reactions is very marked. None but hay fever sufferers will ever react to grass pollen, and grass pollen produces no effect on normal persons." He also says that in asthmatics who are animal-sensitive or bacterium-sensitive, the cutaneous reaction is specific for the sensitizing animal or bacterium.

Baker⁷⁶ did a series of tests on normal children and decided that "In normal children the incidence of protein sensitization is negligible." On the other hand too much reliance must not be placed on a positive reaction.

Sabatini⁷⁷ did cutaneous tests on fifty two apparently normal individuals and found that 19.2 per cent gave positive reactions to one or more proteins.

It is not uncommon for a patient to give a positive reaction to a food that he has never consumed. Highman and Michael⁷⁸ record the case of an orthodox jew who gave strongly positive reactions to pork/

75. *Lancet*. 31.7.20.

76. *Amer. Jour. Dis. Childr.* Feb. 1920.

77. *Il Policlinico Sez. Prat.* April 16. 1921.

pork, oysters, and sturgeon. There is, however, no definite proof that he had never transgressed the law as to these articles of food.

Even if a patient gives a positive reaction to a food that is included in his dietary, one must not conclude that systemic sensitization to that protein is responsible for his symptoms, until exclusion of it from his diet has resulted in their relief. It is depressingly frequent for a patient to react to several proteins and yet to obtain no benefit from the exclusion of them from his diet or environment. A hay fever patient may continue to give a positive reaction to grass pollen throughout the "off-season" for hay fever. At the same time he may suffer from asthma or some allied condition from sensitization to some other protein which must also be detected if a cure of the asthma is to be effected. This illustration may serve as the explanation of certain other apparently irrevelant positive reactions.

A reaction to several proteins, or to a protein which does not enter into the diet, may be explained on/

22. Arch. Derm. & Syph. 1911, 10, 100.
20. Amer. Jour. Hyg. 1911, 10, 100.
21. B.M.A. Meeting, 1911, 10, 100.

on the ground that many proteins from widely different sources may have a closely similar molecular structure or, to quote Highman and Michael,⁷⁹ "The positive reactions are specific in the sense that generically unrelated substances have a chemically identical architecture".

It has also been suggested that multiple sensitization may depend on one antigen giving rise to more than one antibody, or on several different antigens having an identical antibody.

While then, a positive reaction has to be interpreted with caution, a negative reaction does not necessarily imply that there is no sensitization. The reasons for this are:-

- (1) A sensitized patient may fail to react to his specific allergin owing to his tissues having passed temporarily into a phase of non-reactability or anergy. This occurs experimentally in animals after the anaphylactic explosion. Schloss⁸⁰ and others claim that it occurs for periods of twenty six to forty four days after eruptions of urticaria; and according to Mackenzie Wallis⁸¹ it also occurs for/

79. Arch. Derm. & Syph. Nov. 1920.

80. Amer. Jour. Dis. Children. 1920 XIX p.433

81. B.M.A. Meeting. B.M.J. 13.8.21.

for a period of three weeks after severe attacks of asthma and allied conditions.

- (2) Again, the sensitization to a particular protein may be restricted to certain tissues such as the alimentary tract or bronchi and there may be no evidence of it in the skin.
- (3) The sensitizing protein may be so far unisolated or may not be available for test reactions for some other reason.
- (4) The test proteins may have been altered in process of preparation.

To sum up:-

- (1) The cutaneous test lacks full understanding and frequently does not correspond with the other clinical facts.
- (2) In the majority of cases a positive reaction may be taken to indicate sensitization, either to the test protein or to some other protein with a chemical /

chemical affinity to it.

- (3) A series of negative reactions does not rule out sensitization as the basis of the malady.
 - (4) It is an important addition to the means at our disposal for establishing accurate diagnosis and treatment in a certain class of ailments.
-

VI. PROTEIN SENSITIZATION AND HUMAN DISEASE.

It now remains to consider in detail the various pathological states in man that have been ascribed, on grounds varying from tentative speculation to well-proved fact, to sensitization of the organism to foreign protein. Before entering on this subject it will be well to record a few observations that have a special bearing on the subject as a whole.

(1). The influence of Heredity.

The importance of Heredity in human sensitization can hardly be exaggerated. Its influence on the incidence of asthma, migraine, epilepsy, and many cutaneous disorders has long been recognised, but since many of these conditions have been ascribed to sensitization to foreign proteins, investigations on the influence of heredity, have been extended, and it has been found to be an even more constant factor than used to be imagined...

⁸²
Schloss in 80 cases of sensitization in children found an inherited tendency in 59%.

⁸³
Talbot in an inquiry into the relation of food idiosyncrasies to the diseases of childhood found that/

82. *Amer. Jour. Dis. Child.* 1916. XI : 342

83. *Boston Med. & Surg. Jour.* Aug. 29. 1918.

that of 28 cases of asthma, 62% had a family history of Hay Fever, Asthma, Eczema and allied conditions.

⁸⁴
Rackemann in 150 cases of Asthma found a history of heredity in 27%.

⁸⁵
Cooke and VanderVeer investigated 621 cases of human sensitization, most of them Hay Fever sufferers. In 504 cases, in which they were able to obtain a complete family history, they found a direct or collateral ancestral history indicating sensitization in 48%.

In their experience, the more marked the hereditary factor in the toxic idiopathies, the earlier was the age of onset of symptoms of sensitization in those of the off-spring, who happen to inherit what Schreiber has called "The vice of nutrition". They found that in the majority of patients, who first showed symptoms of sensitization after the age of 20, there was no trace of inherited predisposition. Contrasted with the above, we have ⁸⁶ the finding of Harvey Towle that a history of parental sensitization was obtained in 9.5% of a series of 63 apparently normal individuals.

He confirms the observation of Cooke and VanderVeer/

84. Arch. Internat. Med. 1918. XXII. 517

85. Jour. Immun. 1916. I: 201

86 Arch. Derm. & Syphil. Nov. 1920.

Veer that "Sensitized persons transmit to their children not their own specific sensitization, but an unusual capacity for developing bioplastic reactivities to any foreign protein".

Freeman⁸⁷ states that "Heredity is a link which closely binds together the toxic idiopathies", and gives a number of most instructive diagrams which illustrate this factor.

Rolleston⁸⁸ expresses the opinion that the hereditary factor is much more often present in Asthma and allied diseases than is indicated by the available figures, owing to the fact that all signs of sensitization may be escaped by one generation.

In my own experience the difficulty of obtaining an accurate family history bearing^{on} sensitization is very great even in people of intelligence and education, but where it can be obtained, one is strongly impressed by the striking influence of heredity.

No.27 of my series of cases illustrates this and also the difficulty of getting an accurate family history. The assurance that such and such a person was/

87. Lancet. 31st July. 1920.

88. B. M. J. 13th Aug. 1921

was "quite healthy" commonly overlooks the occurrence of a food idiosyncrasy, migraine, or even epileptic fits, or asthma at some period of the individual's life.

(2). The influence of the Nervous System.

Closely linked with the question of heredity is the so-called Neuropathic diathesis which is strongly in evidence in the subjects of sensitization. There is a universal consensus of opinion that the subjects of Asthma and allied disorders are abnormally highly-strung and react to stimuli that would pass unnoticed by the ordinary individual. The phenomenon of dermatography in certain individuals is a good example of this in relation to the skin. Malcolm Morris⁸⁹ states that "Eczema" may break out from purely nervous causes such as acute anxiety. The influence of anxiety is seen in my Case No.16 of Urticaria and in Case No.27 Migraine.

Freeman⁹⁰ states that in a hay fever patient in the hay fever season "A vivid description of a sunny field on a hot still day, will provoke fits of sneezing or the ophthalmo-reaction". Cases of Asthma have been successfully treated by suggestion.

(3)/

89. "Diseases of the Skin" 6th Ed.

90. Lancet. 8.7.1920.

(3) The influence of Infectious Disease.

An attack of infectious disease not uncommonly seems to be the determining factor in rendering a person liable to sensitization. Whether it acts by awaking a latent tendency to sensitization; by inoculating the patient with some residual reservoir of bacterial protein; or by so altering metabolic processes in the liver and other organs that proteins, so altered as to be practically foreign to the organism, pass into the circulation,⁹¹ is a matter of speculation. Weil of Lyons⁹² has found that infants who have been desensitized to an intolerance to milk again become sensitive if they catch measles or other infectious disease.

(4) The influence of various kinds of protein.

That both food and a wide variety of air-borne proteins may be responsible for specific sensitizations is well-established.

Talbot⁹³ stated that during childhood all sensitization was due to foods, but that by puberty, a person, had either developed an immunity to his particular allergin or had attained the wisdom to avoid it, so that after puberty food idio-syncrasies became uncommon., their/

91. Rolleston on Asthma & Allied Disorders. B.M.J. 13.8.21

92. Quoted by Coke. B.M.J. 13.8.21

93. Boston Med. & Surg. Jour. Aug. 29. 1918.

their place being taken by inspired Asthmas and Hay Fever. Talbot's statement is generally speaking in accordance with facts, though the first part of it is an exaggeration. Quite young children do become sensitized to air-borne proteins.

The effect of cooking on the toxigenic capacity of food proteins is remarkable. Stokes⁹⁴ has described two cases of sensitization to unboiled or lightly-boiled egg-white in which hard-boiled egg could be eaten with impunity. The same fact has been noticed in the case of milk and certain vegetables.

The part played by bacterial proteins in sensitization phenomena is difficult to determine. The Von Pirquet and the Mallein tests certainly show a state of specific allergy in Tuberculosis and Glanders. In pyogenic infections on the other hand, cutaneous reactions are comparatively seldom obtained, even in cases such as Bronchitic Asthma, where an autogenous vaccine cures the disease and there is therefore every reason to regard the bacteria, which were grown from the bronchial secretion, as the causal agents of the Asthma.

There is however a very strong impression that sensitization/

94. Arch. of Derm. & Syphil. Nov. 1920. Discussion on papers by Lows & Highman & Michael.

95. Lancet. 31st July. 1920

96. B.M.J. Aug. 13. 1921. p. 235.

sensitization to bacterial protein does play a considerable part in the causation of disease.

Freeman⁹⁵ cured a case of Asthma with inoculations of an autogenous vaccine of bacillus *Pyocyaneus* which he had grown from the patient's stools.

He does not state whether there was a cutaneous reaction to the bacterium. He says elsewhere⁹⁶ with reference to Bacterial Asthma that "Bacterial skin reactions are usually insignificant or absent but do occur sometimes".

Chandler Walker⁹⁷ states that in Asthma bacterial proteins may give a negative reaction and still be the cause of the asthma by infection, not by sensitization. He found that sensitiveness to bacterial proteins is much the same at all ages, the *Staphylococcus Pyogenes Aureus* being the micro-organism most frequently concerned.

Danysz⁹⁸ claims that many chronic diseases like Dermatitis, Urticaria, Psoriasis, Asthma, and many gastro-intestinal disorders are due to anaphylaxis to intestinal bacteria as well as to other proteins, and working on this hypothesis with vaccines prepared from the intestinal flora, he has certainly had some remarkable/

95. *Lancet*. 31st July 1920

96. *B.M.J.* Aug. 13. 1921. p. 235

97. *Boston Med. & Surg. Jour.* Aug 29. 1918.

98. "Origins, Evolution, et Traitement des Maladies Chroniques"

remarkable clinical results.

The association of certain of the Erythemata such as Erythema Multiforme with an unhealthy condition of the tonsils or of the gastro-intestinal tract has been observed by Fordyce who has suggested sensitization to the micro-organisms in the tonsil or bowel as the basis of the affection.

The bacterial flora of Pyorrhoeaalveolaris have likewise been suggested as driving their host to Rheumatism through the gateway of Sensitization.

In the absence of other criteria of specific sensitization, however, the cutaneous reaction remains our only fairly reliable proof of the condition, and we must conclude that infection often works its dire results apart from sensitization and anaphylaxis. Products of autolysis in various organs and tissues are also assumed to produce sensitization and toxæmia, but the condition is a more or less hypothetical one.

(5). The influence of the "Summation" of various factors.

⁹⁹Freeman has pointed out that two or more toxic idiopathies/

idiopathies in one individual may "summate" to produce symptoms of asthma or an allied condition. In such cases the removal of one factor might suffice to cure the asthma. He instanced the case of a woman who was sensitive to cats and also had a bacterial bronchitis. The cure of the latter factor by an appropriate vaccine also relieved her of the toxic idiopathy for cats.

(6) The influence of the frequency, duration and degree of exposure to foreign protein.

The above factors are in evidence in hay fever in which the only pollens of practical importance are those which are produced at one season in great quantity, and are light enough to be easily wind-borne. ¹⁰⁰ Coke has pointed out the fact that the foods which most often produce sensitization are those which are partaken of on rare occasions and in considerable amount, e.g. egg-white in children with diarrhoea, cow's milk in the breast fed infant, strawberries, oysters, and lobster in the more mature.

Prolonged contact with large amounts of protein result in occupational asthmas of the baker, miller and hostler.

HISTAMINE TOXAEMIA AS A CAUSE OF
ASTHMA AND ALLIED DISORDERS.

Coke¹⁰¹ has pointed out that Histamine has been found by Eustis in the stools of three asthmatics out of ten. Bacteria have been isolated from the intestine that have a special power of forming Histamine from the proteins or protein-derivatives of food. It is, therefore possible that absorption of Histamine or closely related substances from the bowel may be the cause of many cases of asthma, urticaria, and allied disorders which cannot be ascribed to any specific protein sensitization.

The phenomenon of Auer described on page 58 may possibly furnish us with an explanation of some of the local exacerbations that occur in Gout and Rheumatism, Dermatitis, and other skin conditions, as well as various more or less temporary functional derangements. It seems possible that the exacerbation of "Rheumatism", that so often heralds a change in the weather or follows a change of climate, may, in some cases at least, be due to a systemic sensitization to certain airborne proteins, such as moulds, which/

¹⁰¹. B. M. J. Aug. 13. 1921 p. 236.

which are undoubtedly more abundant under mild, moist atmospheric conditions and are probably inhaled in considerable amount.

I have only tested one case with this sensitization to moulds in view and got no reaction.

Case 31. Mrs E.C. a native of Edinburgh but settled in a West of Scotland watering place for one year. Since going to her new home has suffered from frequent headaches with tenderness of scalp. A return to Edinburgh rids her of the headaches at once, and they recur when she goes back to the West. Moulds grow rapidly and abundantly on bread, cheese, boots etc., in her house.

Cutaneous test with moulds from cheese negative.

One case of course proves nothing one way or the other.

THE "CRISE HÉMOCLASSIQUE" OF WIDAL AND ABRAMI.

This blood crisis has been described by Widal and/

¹⁰² and Abrami as occurring in Asthma and allied disorders. It is characterised by a temporary leucopenia, a fall in arterial blood pressure, hyperviscosity, and a diminution of coagulability of the blood, which precede the attack of Asthma or Migraine.

The patient is unconscious of any symptoms when this blood crisis is going on. It is stated to occur in Anaphylactic shock, protein shock, asthma, urticaria, migraine, epilepsy, paroxysmal haemoglobinuria, malaria, and in wound shock from absorption of autolytic products.

Eosinophilia.

Eosinophilia has already been referred to in considerable detail on page 43.

It occurs in asthma and hay fever both in the secretions, and in the peripheral circulation; in epilepsy and some cases of migraine; intestinal worms and hydatid disease; after an injection of tuberculin; in urticaria; pemphigus, and dermatitis herpetiformis.

Its exact value as a clinical sign of sensitization to foreign protein is still disputed but its presence may be a valuable indication to investigate a sensitization to foreign protein as a possible basis for an obscure clinical condition.

I/

I propose, for greater convenience, to arrange the diseases, which will be dealt with, in groups according to the system on which the main emphasis of symptoms is laid.

1. GENERAL.

- (1). Serum Sickness.
- (2). The exanthemata.
- (3). Paroxysmal Haemoglobinuria.
- (4). Parasitic Infestations.
 - (a) Ascaris and other intestinal worms.
 - (b) Taenia echinococcus (Hydatids).
- (5). Gout and Rheumatism.

2. THE RESPIRATORY SYSTEM.

- (1). Hay Fever.
- (2). Asthma.
- (3). Rhinitis.
- (4). Bronchitis.

3. THE ALIMENTARY SYSTEM.

- (1). Vomiting.
- (2). Diarrhoea.
- (3). Mucous Colitis.

4. THE NERVOUS SYSTEM.

- (1). Irritability.
- (2). Insomnia.
- (3). Epileptiform Convulsions.
- (4). Migraine.

5. THE INTEGUMENTARY SYSTEM.

- (1). Urticaria.
- (2). Angioneurotic Oedema.
- (3). Dermatitis Seborrhoeica, etc.
- (4). Dermatitis Herpetiformis.
- (5). Erythema.

1. GENERAL DISEASES.(1). Serum Sickness.

This condition has already been considered in considerable detail. There is a tendency to regard it as a rather trivial affection, but my own personal experience of the disease as a result of sensitization

two/

two years before the toxigenic dose, has taught me that it is not a condition that should be lightly inflicted on a patient.

A severe urticarial eruption, oedema, and high temperature form a sufficiently unpleasant complication to an acute infectious disease, but add thereto a multiple arthritis involving the limbs and temporo-maxillary joints, an inflammatory infiltration of the muscles of the tongue rendering every movement of the organ acutely painful, tenderness of certain nerve trunks and almost complete deafness, and the cure becomes worse than the disease.

I am convinced therefore that every reasonable precaution should be taken, especially in potentially sensitized patients, who are so ~~common~~ nowadays, to bring about desensitization before giving a therapeutic dose of serum. ¹⁰³ Ker recommends that we should assume sensitization for ten days to three years after a previous dose of serum and take measures to counteract it.

These measures will be considered in the chapter on desensitization at the end of this thesis. Fortunately serum sickness has become less common in recent/

103. "Infectious diseases". 2nd ed.

recent years. Ker states that prior to 1909, 25% of his serum injections were followed by serum sickness, whereas in 1916 - 17 of 1608 patients injected only 8.2% had serum sickness. This he attributes to a higher potency of antitoxin being contained in a smaller bulk of serum.

(2). The Exanthemata.

The incubation period and other characteristics of the exanthemata are considered by Von Pirquet and Schick to be due to an anaphylactic reaction. They hold that the Antigen per se does not produce toxæmia. The incubation period is the time required for the production of antibodies. These when formed interact with the antigen, and apotoxin is produced, the symptoms of the disease beginning when the organism is flooded with apotoxin.¹⁰⁴

(3). Paroxysmal Haemoglobinuria.

This condition has been ascribed by some clinicians to auto-anaphylaxis. One of the commonest causes is chilling of the surface of the body by cold air, a cold bath, or even holding the hands in cold water. The haemoglobinuric paroxysm is preceded by the "Crise Hémoclasique".¹⁰⁵

Schiassi/

104. C.B. Ker. "Infectious Diseases". 2nd Ed.

105. Semaine Médicale. 1913. p. 613.

¹⁰⁶
 Schiassi has found that the paroxysm does not necessarily culminate in haemoglobinuria, provided that the application of cold be duly modified. In such a case the main features of the attack were a transient leucopenia, malaise, nausea, and a rise of temperature. There does not appear to be any real proof that the condition is related to the anaphylactic mechanism.

(4). Parasitic Infestations.

(a) Intestinal Worms.

There seems to be good reason to believe that Urticaria, asthma, convulsions, and other so-called reflex effects of Ascaris and other intestinal worms are really due to sensitization of the organism to a protein substance which is believed to be secreted by the worms.

Eosinophilia is a very constant and significant feature. The work of Herrick with aqueous extract of Ascaris has already been alluded to.

¹⁰⁷
 Schwartz believes that parasitic worms secrete toxic substances which are absorbed by the host and that these account for the so-called reflex symptoms in/

106. *Il Policlinico Sez. Med. Nov.* 9 & 10.

107. *Arch. Internat. Med.* 26: 431 (Oct.) 1920

in helminthiasis.

Freeman¹⁰⁸ states that worms when handled or dissected for some time, give rise to all the nasal and eye symptoms of an air-borne toxic idio-pathy and alludes to the fact that children of a toxic-idiopathic taint sometimes get asthma as a consequence which clears up after the removal of the worms.

The importance of the latent toxic idiopathic taint probably explains why only a small proportion of people infested with worms manifests serious symptoms.

(b) Hydatid disease.

This results from infestation with the taenia echinococcus.

Indications of specific sensitization are found in eosinophilia; urticarial eruptions should a cyst rupture; Casoni's reaction to the intra-dermal injection of 0.5 cc. of clear hydatid fluid from an ox or sheep; and a cutaneous reaction to the same fluid.

In 1909 Chauffard, Boidin, and Laroche¹⁰⁹ brought about anaphylaxis with injections of fluid from hydatid/

¹⁰⁸. Lancet 31.7.20.

¹⁰⁹. Compt. Rend. Soc. Biolog. 1909. LXVII. 32.

Hydatid cysts.

¹¹⁰ Pontaro states that the fluid of hydatid cysts is antigenic for the human organism and that a person not suffering from hydatid disease can be sensitized to it, while a high percentage of patients with hydatid disease give a positive cutaneous reaction to fresh cyst fluid. He believes that the few negative reactions in cases of hydatid disease are due either to calcification or other abnormal thickening of the cyst wall or, more commonly, to suppuration of the cyst contents.

¹¹¹ Serra recommends the employment of the intradermal test as a safe and accurate diagnostic measure.

Here then, sensitization of the tissues to the secretions of the taenia echinococcus has provided us with a valuable and specific diagnostic test.

(5) Gout and Rheumatism.

These two conditions are considered together, as their relation to protein sensitiveness is still purely speculative.

¹¹² Rolleston has recently suggested that gout may bear some relation to sensitization of the body to foreign/

110. *Il. Policlinico Surg. Med.* Nov. 1, 1920.

111. *Il. Policlinico Surg. Chir.* Jan. 15, 1921

112. *B. M. J.* Aug. 13, 1921

foreign proteins. He points out that gout is undoubtedly a vice of protein metabolism, that is markedly hereditary, and often associated with food idiosyncrasies. It is also not uncommonly associated with Asthma, Migraine, Dermatitis, and other allied diseases.

It seems possible that some cases of rheumatism may be ascribed to the same cause. The joint and muscle pains in serum disease are suggestive of a possible connection.

Mackenzie Wallis¹¹³ has described a case of intermittent hydrarthrosis in which the patient gave a cutaneous reaction to his own joint effusion.

The possibility that moulds may be the toxic agents in some cases, has been indicated above and the possible influence of Auer's phenomenon has also been mentioned.

Most of this is purely speculative and only extensive clinical observation and experiment can decide whether our hypotheses are of value or no.

113. B.M.J. Aug. 13, 1921. p. 235.

2. THE RESPIRATORY SYSTEM.

(1). Hay Fever.

The steps by which hay fever came to be recognized as a phenomenon of sensitization have already been related.

The fact that the specific antigen, viz. the pollen of certain flowering grasses, chiefly Rye and Timothy grass, is only operative during a short period of the year, separates the condition from all other sensitization diseases, and has simplified its study.

Specific cutaneous and ophthalmic reactions for the prevalent pollens are very constant, and a hereditary taint can be traced in a very large proportion of cases.

A highly-strung nervous temperament characterises many of the sufferers.

Eosinophilia of the peripheral blood and also of the nasal secretions is always present. Hay Fever is often associated with definite spasmodic asthma which may be the direct result of pollen sensitization due to sensitization to some other protein such as horse/

horse dander.

Other phenomena of sensitization such as urticaria, dermatitis, or migraine are often met with in hay fever patients and, like asthma, they may be due to the pollen or to some other protein.

Antibodies to the pollen protein are demonstrable in the blood of Hay Fever patients.

Passive anaphylaxis of animals to pollen can be induced and, to a certain extent, passive immunization of sensitized subjects can be procured, by the serum of immunized animals.

Some individuals develop a natural immunity to the pollen after passing through several attacks of hay fever.

90% of the sufferers can be rendered completely immune or their susceptibility greatly reduced by a course of inoculations with the extract of the specific pollen.¹¹⁴

This immunity lasts for about twelve months, so that patients can be carried through one summer after another in comfort if they undergo an annual course of inoculations a few weeks before the grass comes into flower. On the other hand an excessive dose of pollen/

pollen extract may produce all the symptoms of the disease in an extreme and serious degree.¹¹⁴

In America the hay fever season, which occurs in June, when the grass is in flower, is succeeded in the Autumn months by the "Fall Fever", which although identical with hay fever in symptomatology is caused by the pollens of Ragweed and of Golden Rod, a member of the Compositae.

¹¹⁵
Rackemann has carried out a careful investigation into ragweed fever in 91 cases. He found that though the local and general reactions in man to extracts of ragweed pollen are closely similar to those of artificial anaphylaxis, and he was able to cure or greatly relieve two thirds of his cases by inoculations of the pollen extract, ragweed fever differs from them in the fact that (a) the presence of specific antibodies in the blood of ragweed fever patients is doubtful; and (b) it is impossible to sensitize guinea pigs to ragweed pollen.

He suggests that ragweed fever depends on a mechanism which is not anaphylactic, but is rather to be classed with drug idiosyncrasies.

(2)/

114. *Ann. Intern. Med.* June 10, 1911

Freeman Lancet Sept. 16, 1911; April 25, 1914; & July 31, 1920.

115. *Boston Med. & Surg. Jour.* Vol. CLXXII No. 10.

(2). Asthma.

Although certain authorities consider that every case of asthma is as much a manifestation of sensitization to foreign protein as is hay fever, the majority of physicians are not prepared to commit themselves any further in that direction than can be justified by definite proof. At present our proof that a case of Asthma is due to sensitization to foreign protein must rest on four factors.

(a) A personal or family history of the toxic idiopathic taint.

The question of heredity had already been gone into.

The frequent association of Asthma with other idiopathic diseases such as urticaria had long been recognized. John Thomson in an analysis of 100 cases¹¹⁶ of asthma in children found that 26 had had Eczema in infancy; eight urticaria; two ichthyosis; one psoriasis; two fits; two hay fever; and several had idiosyncrasies for eggs and other foods.

(b) A cutaneous reaction to a protein that has access to the patient.

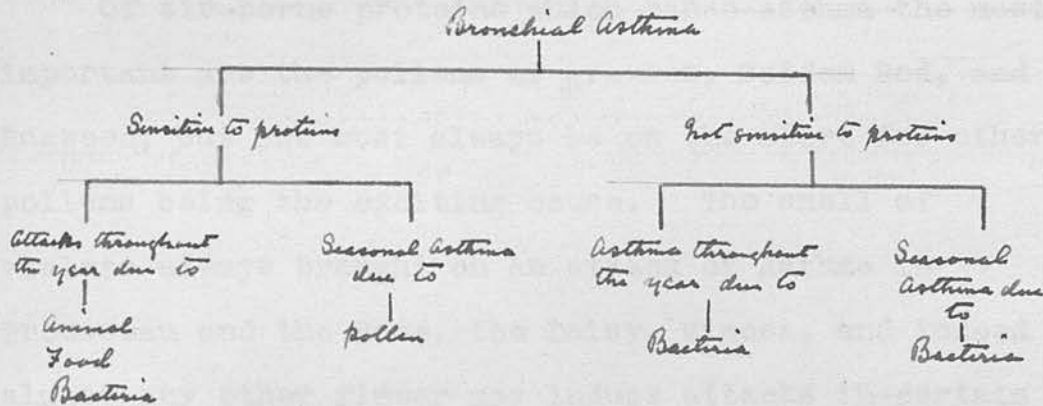
(c) the beneficial result of excluding that protein from the patient and the provocation of a relapse by re/

116. *The Clinical Study & Treatment of Sick Children* p.521

re-exposure.

(d) the curative effect of a specific or non-specific method of desensitization.

We have seen that in only about 50% of all cases of Asthma can a cutaneous reaction be obtained indicating sensitization to a foreign protein. Chandler Walker¹¹⁷ has made the following useful classification from a study of 400 cases of Asthma.



In infancy and childhood, foods, especially eggs and milk, are the chief cause of Asthma.

As childhood merges into adolescence, the air-borne proteins take the chief share in producing sensitization ./

¹¹⁷. Jour. R. N. Med. Serv. Oct. 1917.

sensitization. In later life bacterial infection is the main cause, and in no case of asthma which commenced after the age of 50, did Chandler Walker¹¹⁸ obtain a reaction to protein. It seems probable that as knowledge increases, more and more cases of asthma, which at present fail to react to the ordinary protein tests, will be found to be associated with sensitization to foreign protein or to absorption of split protein derivatives of the Histamine type.

Of air-borne proteins which cause asthma the most important are the pollens of grasses, Golden Rod, and Ragweed, but one must always be on the alert for other pollens being the exciting cause. The smell of violets always brought on an attack of Asthma in Trousseau and the Rose, the Daisy, Mimosa, and indeed almost any other flower may induce attacks in certain individuals.

In chemical factories the dust of powdered ipecacuanha has been found to induce asthma in some of those exposed to it, but whether ~~this~~ is due to protein sensitization or to the action of a chemical irritant, I have not been able to ascertain.

Chandler Walker¹¹⁸ has described a case of asthma in a coffee-bean sifter who gave a positive reaction to/

¹¹⁸ Boston Med. & Surg. Jour. Aug 29, 1918.

to coffee bean protein.

One of the commonest industrial causes of asthma is found among bakers and millers, who become sensitized to the flour protein which they inhale.

Of animal emanations, the protein content of which induces asthma by inhalation, the most common and important is the horse's. Not only does the dander of the horse produce the attack, but the urine and faeces are also potent, and Freeman¹¹⁹ quotes a case where a horse-flesh sausage, unwittingly partaken of, brought on an immediate paroxysm. The great danger of horse-serum injections in such cases has been mentioned. A person who is sensitive to horse, is also sensitive in varying degree to other members of the Equidae, - Onega, Zebra and Donkey.

If the horse is the most common animal cause of asthma, the dog is the least common, but almost every one of the domestic animals may be a cause of sensitization of susceptible human beings, who are brought in contact with them. The down and feathers of chickens and other fowls have a similar capacity, so that in searching for the cause of asthma, one has to be extremely alert to all the possible animal sources of sensitization. Many remarkable illustrations are on record/

¹¹⁹. Lancet. July 31. 1920. p. 232 et seq.

record of the extraordinary degree to which animal sensitiveness may be carried. There is the horse sensitive man who gets asthma if he is in the same room as a person who has been riding; the rabbit sensitive sportsman who cannot hit a bird if there are rabbits in the neighbourhood; and the cat-sensitive person in whom the proximity of a cat induces a paroxysm of asthma. The down quilt and feather pillow must always be regarded with suspicion.

¹²⁰ Coke states that human hair and dandruff may be the source of "foreign" sensitizing protein in some individuals and that skin reactions to human hair are obtained in these cases.

It is important to note that there is often no feeling of antipathy on the part of the patient to the sensitizing animal and he is quite unconscious of its baleful influence over him.

Of eleven asthma patients¹²⁰ who became sensitive to proteins after the age of 40, Chandler Walker¹²¹ found that four were bakers and reacted to wheat protein; one was a coffee-bean sifter and reacted to coffee bean; one an hostler reacted to horse dander; so that/

120. B.M.J. March 12. 1921 p.373

121. loc. cit.

that 50% were caused by inspiration of proteins incurred in the course of their occupation.

The influence of bacterial infection in relation to sensitization has already been discussed, and the curative effects of autogenous or other properly selected vaccine treatment in many cases of asthma has been mentioned.

Freeman¹²² states that having, as the result of successful treatment of asthma with bacterial vaccines, come to the conclusion that the asthma was in these cases the remote effect of the bacterial infection, he has now come to believe that this bacterial asthma is a toxic idiopathy to the microbial endotoxin. He bases his belief on (a) The occurrence of bacterial asthma in families of the toxic-idiopathy taint.

- (b) a bacterially specific ophthalmo-cutaneous reaction which is sometimes obtained to the extracted bacterial endo-toxins of the bronchial asthmatic.
- (c) the curative effect of appropriate doses of the specific vaccine.
- (d) an excessive dose of the vaccine will produce in the subject of bronchial asthma the same symptoms as an excessive dose of pollen extract or horse protein produces in hay fever and horse asthma subjects respectively, viz. violent asthma, oedema, and urticaria.

Chandler/

¹²³
Chandler Walker while attributing about 50% of asthma cases to bacterial agency, considers that many of them are due to infection apart from sensitization to the bacterial protein.

¹²⁴
Caulfield's experience of asthma among soldiers in Toronto, led him to the conclusion that bacterial skin reactions in asthma were of little or no value and he doubts if bacterial protein has an etiological importance in asthma equal to that of other proteins.

¹²⁵
In Walker's experience the staphylococcus pyogenes aureus was the micro-organism most frequently concerned in the causation of bacterial asthma, but ¹²⁶Sanford at the Mayo Clinic, Rochester failed to get a single positive reaction to staphylococcus pyogenes aureus and albus in 365 cases tested.

It would seem therefore that tests with bacterial protein are of little value in asthma and that the practical plan of dealing with a case that fails to react to ingested and airborne proteins is to attempt treatment with an autogenous or an appropriate stock vaccine.

(3) Rhinitis.

John/

123. Boston Med. & Surg. Jour. Aug 29. 1918.

124. Jour. Am. Med. Assoc. 1921 LXXVI. 1071

125. Collected papers of the Mayo Clinic. 1919. VI. 1201

John Thomson¹²⁶ describes in babies an irritative condition of the upper respiratory passages which is often described as "A dry cold". It is characterised by rubbing the nose, snuffling breathing, and sneezing. He considers the condition to be analogous to the irritation of the nose that is seen in the anaphylactic guinea pig.

(4) Bronchitis.

Many victims of the toxic idiopathies are subject to "Bronchial Attacks" which do not justify the name of Asthma though they are probably due to a slight degree of bronchial spasm. My Case No.16 of Urticaria illustrates this.

John Thomson¹²⁶ describes in babies a condition of the lower respiratory passages which he considers to be analogous to the Rhinitis just described. There is rapid breathing without dyspnoea, wheezing and a croupy cough ending sometimes in a regular asthmatic seizure. Like the rhinitis, it is characterised by sudden, apparently causeless onset, and rapid and complete recovery.

126. *The Clinical Study & Treatment of Sick Children*. 3rd Ed.

CASES OF ASTHMA.

No.12 Peter Simpson aged 11 under the care of Dr Fowler in the R.H.S.C. Edinburgh. His mother is asthmatic. He himself has had asthma since he was six years old, the attacks being most frequent in summer and autumn.

Since admission to hospital he has had no attack.

His home is close to a farm and he plays in the steading.

4.2.21. Cutaneous tests to milk, egg white and yolk, lamb, pork, herring, haddock, beef, oat, rice, wheat, potato, all negative.

7.2.21. Cutaneous tests to horse dander, sheep-wool, cattle hair, cat's hair, dog's hair, and goose feather all negative.

Pollen of Red-top grass +

Orehard grass + —

Timothy, June, Goldon Rod and Ragweed. —

A few days later he returned to his home and again got asthma which indicated that he was sensitive to/

to something in the environment of the farm. His sensitiveness to pollen might cause his asthma if he played among the hay. On the other hand he may also have been sensitive to some other protein, e.g. chicken feather, which I had not tested him for, I was unable to follow up the case.

No.14. Dorothy Simonoff aged $4\frac{1}{2}$ under the care of Dr McNeil in the R.S.C.H. There is a history of repeated attacks of asthma since January 1920. The mother suspects egg, soups, and banana as being the cause.

10.2.21. Cutaneous tests for egg white and yolk, milk, beef, lamb, potato, wheat, rice, all negative. I had not an opportunity of doing further tests.

No.19. A baby aged 12 months under the care of Dr J.S. Fowler at the R.H.S.C.

History: The child commenced to suffer from asthma in January 1921, and has had almost constant wheezing with exacerbations ever since. It's diet includes milk, cocoa, soup, rice, farola, custard, eggs, potato, meat, fish, bread/

bread, butter.

22.3.21. Cutaneous tests for

Egg white ++

Egg yolk +

Oat +-

Milk, potato, rice, wheat, beef, all -.

Unfortunately the child developed pneumonia the day after the tests, and although egg and oats were eliminated from the diet, it succumbed to the pneumonia which Dr Fowler thought was probably tuberculous..

3. THE ALIMENTARY SYSTEM.

Under this system it is not proposed to discuss food sensitization per se but rather to indicate certain morbid conditions of the digestive tract that are believed to be attributable to its sensitization to foreign protein.

Vomiting, diarrhoea and the passage of blood, and congestion of the liver are marked features of experimental anaphylaxis in the dog. The ingestion of the specific allergin by a food-sensitive person may result in immediate vomiting and perhaps diarrhoea and these are commonly followed by urticaria and even asthma. Freeman¹²⁷ has shown that ingestion of pollen in "doctored" beer by an unsuspecting hay fever patient resulted in nausea and diarrhoea.

Talbot¹²⁸ states that sensitization to cow's milk is usually manifested by vomiting, and that egg is a common cause of gastro-intestinal disturbance.

John Thomson¹²⁹ gives a good description of idiosyncrasy to cow's milk. He states that it first appears two or three months after birth, and is usually/

127. *Lancet*. 31.7.1920. p.229

128. *Boston Med. & Surg. Jour.* 29.8.1918.

129. *Clin. Study & Treatment of Sick Children*. 3rd Ed. p.204

usually recovered from within a few months, but may persist in a modified form. He distinguishes two types.

In the first the child develops urticaria and asthma within fifteen minutes of a feed of cow's milk.

In the second, the onset of the symptoms is delayed for one to five hours, then the child becomes pallid and drowsy, is ill at ease, vomits, and becomes collapsed.

Sometimes there is diarrhoea with mucous in the stools, fever and glycosuria.

Laroche, Richet, and Saint-Girons¹³⁰ writing on "Alimentary Anaphylaxis" claim an anaphylactic origin for certain cases of chronic gastro-enteritis, loss of flesh being a prominent symptom. They quote a case of intolerance for eggs in which examination of the stools revealed deficiency of pancreatic secretion. Under the administration of pancreatic extract, the boy was able to eat eggs with impunity.

Danysz,¹³¹ as already mentioned, attributes many gastro-intestinal disorders to anaphylaxis to intestinal bacteria.

Auld¹³² has reported the successful treatment of "Cyclic gastro-intestinal attacks" with peptone.

A/

¹³⁰. Extracted Jour. Am. Med. Assoc. 14.8.1920.

¹³¹. Danysz. "Origin, Evolution et Traitement des Maladies Chroniques".

¹³². B.M.J. 14.5.1921. p.698.

A case of cyclic vomiting will be noticed in the child of Case No.27 "Migraine and mucous colitis".

Eosinophilia is not uncommon in mucous colitis and the neuropathic diathesis is exceedingly common.

These points are highly suggestive of sensitization to foreign protein forming the basis of many cases of vomiting of the cyclic variety, diarrhoea, mucous colitis, and chronic indigestion, but so far little definite proof can be offered in support of the suggestion.

Case No.23, - a man suffering from post-dysenteric, mucous colitis, was tested with autogenous bac. coli and streptococcus and gave no reaction.

Case No.27, - migraine and mucous colitis, gave no reaction to any test protein. Details of the case are given under migraine.

4. THE NERVOUS SYSTEM.

Attention has lately been directed to various unexplained functional disorders of the nervous system in the hope that some of them, at least, may be explainable in the light of the new knowledge of the toxic idiopathies.

The central nervous system undoubtedly plays an important part in the production of anaphylactic shock in animals, as has already been shown.

In the human subjects of protein sensitization as exhibited in asthma and allied disorders, a very delicately balanced nervous system is an almost constant characteristic. The same characteristic is found in migraine, epilepsy and certain other affections such as insomnia. They too are markedly hereditary and they not uncommonly coexist with asthma, gout, dermatitis and other manifestations of the toxic idiopathy. The sudden almost explosive onset and the abrupt termination of migraine are also significant. Ascariasis is a recognized cause of epilepsy in children.

Eosinophilia is frequently present in both migraine and epilepsy, and either condition may be ushered/

ushered in by a fall in the number of leucocytes from 12,000 to perhaps 4,000 per cmm. and a drop in the arterial blood pressure.¹³³

Richet's observation that chloral inhibits anaphylactic shock in sensitized guinea pigs, has an interesting and suggestive parallel in certain cases of infantile convulsions, which, although unyielding to bromide administration, are readily controlled by chloral in full doses.¹³⁴

The late Professor John Wyllie used to teach that for infantile convulsions there is nothing so effective as chloroform and a warm bath.

Intravenous administration of peptone, on the same principle on which it is used for asthma, has in the hands of Auld¹³⁵ resulted in the relief of many cases of migraine and epilepsy.

All these facts are strongly suggestive of sensitization to foreign protein being manifested in some individuals by migraine and epilepsy, and perhaps by certain other functional disorders. John Thomson considers it to be responsible in children for many cases of general irritability, restlessness and fretfulness, insomnia and probably certain types of convulsions, especially that amenable to chloral mentioned above.

133. Vidal & Abrami. *Presse Medicale*, 1914. p. 525.

134. John Thomson. *Clin. Study & Treatment of Sick Children* 3rd ed. p. 546.

135. *B. M. J.* 14.5.21. p. 698.

ILLUSTRATIVE CASES.

Pagniez¹³⁶ has recorded the case of a man who suffered from severe migraine attacks which were attributed to chocolate. The attacks were ushered in by the "Crise hémoclasique".

Case No.20. Dr E.G. - invariably suffered from migraine if he indulged in coffee, a single small cup being sufficient to bring on an attack. Incidentally he was very fond of coffee.

21.3.21. Cutaneous test for coffee protein negative.

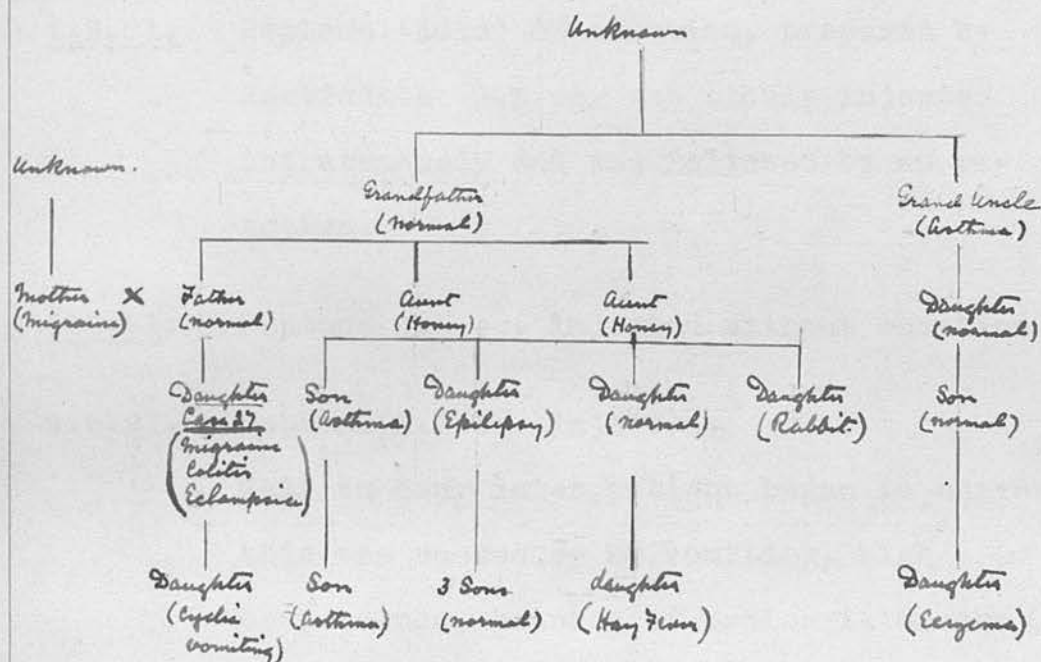
Case No.27. Mrs B. - had suffered from migraine with well-marked visual disturbance in adolescence. This passed off but was succeeded by severe mucous colitis which persisted for 15 years and is still liable to recur. In her second pregnancy she had albuminuric eclampsia. Three years ago when run down through war-strain and under-feeding she began to suffer from migraine again, the attacks being characterised by intense hemicrania and uncontrollable vomiting. The attacks synchronise with/

136. *Presse Médicale* Nov. 19. 1914.

with the monthly period, but when she is over-strained they may also occur about the middle of the month. An attack usually lasts for about 36 hours during which time she is utterly prostrate. There is no abnormality in teeth, eyes or other organs.

She is extremely sensitive to drugs and vaccines, the average dose of either being toxic for her.

Her family history shows a well-marked toxic idiopathic taint and though by no means complete, is given here as an instructive example of hereditary influence.



Only those members of the family who are known to have suffered from a toxic idiopathic condition have been entered in the diagram. Many have shown no evidence of the taint.

- 30.3.21. Cut. tests for Oats, onion, pork potato, rice, cheese, chicken, egg, beef, sole, walnut, wheat, haddock, halibut, herring, milk, lamb - all negative.
- 1.8.21. Cut. tests for carrot, turnip, cabbage, pea, tomato, banana, strawberry, tea, coffee, cod, almond, barley, bean, celery, chicken feather, horse dander, Staphylococcus pyogenes Aur. Alb. and Citr. Streptococcus viride and haemolyticus all negative.
- 1.8.21. Peptone (Auld) 5% solution, prepared by Martindale 0.3 cc. was slowly injected intravenously and was followed by no reaction.
- 4.8.21. Peptone 0.5 cc. injected without reaction.
- 9.8.21. Peptone 0.7 cc. injected.
Half an hour later patient began to shiver; this was succeeded by vomiting, high temperature, patches of urticaria on the thighs and severe headache of the usual type. She was prostrate for two days with slight fever, nausea and vomiting, and headache. The next period, a week later, passed/

passed without any headache, a unique occurrence.

1.9.21. Peptone 0.2 cc. intravenously without reaction.

6.9.21. Peptone 0.4 cc. " " "

Further injections were temporarily suspended owing to an attack of colitis.

At the next period patient suffered from headache, nausea and vomiting but these were not so severe as to prevent her carrying out her duties.

Treatment has been resumed with a 2% solution of peptone with Lugol's solution of Iodine added to it to reduce its toxicity.

5. THE INTEGUMENTARY SYSTEM.

In no department of Medicine has the study of protein sensitization raised higher hopes than in diseases of the skin, and during the fourteen years since Wolff-Eisner first suggested that urticaria is a result of the anaphylactic mechanism, considerable progress has been made in elucidating some of the baffling problems of dermatology. Urticaria and Angio-neurotic Oedema will be considered together as they are closely linked by being dependent on identical etiological factors and a close clinical similarity, the one passing almost imperceptibly into the other through Urticaria Gigas and Urticaria Oedematosa. Long before the days of Anaphylaxis, the urticarias were well known to be associated with an idiosyncrasy for certain foods, more especially eggs, shell fish, lobsters, strawberries, pork, pickles, and porridge. It had been recognized that they frequently ran in families and were often associated with hay fever, asthma, migraine, infantile convulsions and other manifestations of the neuropathic diathesis. They were often seen in association with worm/

worm infestation especially ascariasis, and with hydatid disease when the cyst ruptured. They were known to be one of the most constant manifestations of serum sickness and were also a common symptom of intolerance for certain drugs such as Copaiba and more recently Salvarsan. They were also associated with digestive disorders, with uterine and ovarian disorders of women, as well as with gout, rheumatism, purpura and occasionally with albuminuria. As in asthma, eosinophilia was very constantly present both in the peripheral circulation and in the local lesions and there was often a very remarkable response to the subcutaneous injection of adrenalin, an attack subsiding with dramatic suddenness.

Two explanations of the condition held the field without shedding much light on its actual mechanism.

One ascribed it to a reflex vaso-motor disturbance of the skin as a result of irritation of the terminal branches of the vagus in the alimentary mucosa or elsewhere.

The other theory was that a toxin circulated in the blood stream which caused local death of the cells of the cutis or irritation of the walls of the capillaries followed by congestion and exudation of serum.¹³⁷

When therefore, Wolff-Eisner¹³⁸ suggested that urticaria/

137. Malcolm Morris. *Diseases of the Skin* 6th Ed. p. 90.

138. Ueber die Urticaria vom Standpunkte der neueren Erfahrungen
Dermatolog. Zeitschr. 1907.

urticaria was explainable on the ground of hypersensitivity to foreign protein, he provided a clue not only to the imperfectly understood etiology of urticaria but to the many morbid conditions already described, with which it is so closely interwoven.

Since then much of the pioneer work on protein sensitization in man has centred round the urticarias.

The subject of urticaria has been so repeatedly referred to in connection with the other toxic idiosyncrasies that it is not necessary to recapitulate here.

Some of the most important work on it has been done by Schloss in America.

In 1912¹³⁹ he reported his classical case of a boy, in whom severe urticarial lesions were produced by eggs, almonds, and oatmeal. The sensitiveness to egg and oatmeal was acquired, i.e. it was not apparent on the first occasion on which they were eaten. That to almonds appeared on the first occasion that they were eaten. There was a positive cutaneous reaction to all these articles and no reaction to other proteins.

Guinea pigs were sensitized to ovo-mucoid, one of the proteins of egg-white, by intra-peritoneal injections of the patient's serum, and then rendered anaphylactic by a small injection of ovo-mucoid.

139. Amer. Jour. Dis. of Childr. June 1912.

It is not asserted that all urticarial eruptions are dependent on sensitization to foreign protein, and according to Highman and Michael¹⁴⁰ "No type of urticarial lesion, except those of presumably anaphylactic origin, give cutaneous reactions or respond to supra-renal extract".

The cutaneous test is of great value in determining the specific protein responsible for the urticaria and its employment has led to the detection of many hitherto unsuspected food substances as being the causal agent in certain cases. Engman and Wander¹⁴¹ in a recent paper on "The Application of Cutaneous Sensitization to diseases of the skin" state that 79% of their cases of urticaria gave a positive skin reaction.

140. Arch. of Derm. & Syph. Nov. 1920.
 141. idem. Mar. 1921.

C A S E S.

Case No.11. M.J., aged 20.

Attending the Skin Department, R.I.E.

Urticarial papulosa of eleven years duration. She enjoyed good health until the age of 10 when she began to suffer from the present trouble and has suffered ever since in spite of frequent attendance at the Skin Department of the R.I.E. She thinks that she suffers most in September and in hot summer weather.

Her diet consists largely of milk, eggs, fish, bread, etc., cabbage, turnip, carrots, tomato, apples, oranges and bananas.

She thinks that meat makes the eruption worse, and that porridge upsets her stomach, but does not affect the skin. Bananas also "upset her stomach".

In November 1913 eosinophils were 15%.

In October 1914 she had an attack of asthma, the only occasion on which she has suffered from it.

1.2.21. There are papules on the arms and all over the body. These are very itchy especially before they come out.

Cutaneous/

Cutaneous protein tests for Haddock, herring, milk, lamb, beef, cheese, egg white and yolk, oat, wheat - all negative half an hour after inoculation.

When patient returned on 15.2.21 she stated that four hours after inoculation there was a marked reaction to haddock, milk, and lamb which was still evident the next day.

See Freeman's statement. that reactions are sometimes delayed. page 63.

15.2.21. Cutaneous tests for pork, potato, rice, haddock, salmon, sole, walnut, onion, parsnip, peanut, almond - all negative.

I directed her to refrain from milk, haddock and mutton entirely.

26.2.21. Has continued to take milk in tea and is evidently not prepared to give it up.

26.2.21. Cutaneous tests for haddock, milk and lamb repeated. Fresh tests for banana, sheep's wool, goose feather, strawberry, cabbage, turnip, carrot, tomato, tea.

No reaction early or late.

Patient reported that there was no improvement in her condition as the result of alterations in diet.

She/

She is however an unreliable patient and cannot be relied on to carry out instructions. Whether the delayed reactions to milk, haddock, and lamb were of any significance I cannot say, but there is good reason to think that the patient is a case of sensitization to protein.

Case No.13. Wm. B., aged 4.

Urticaria papulosa. Repeated attacks since he was six weeks old. Never breast fed. Was started on cow's milk and when the urticaria began was put onto Allenbury's food for two months, then onto Horlick's malted milk. Now gets an ordinary general diet including milk, eggs, porridge, and fish, but not butcher's meat as he does not like it.

The father knows of no article of diet that aggravates the skin condition.

General health is good except that he is liable to alarming "fainting fits" which last for 10 minutes or so if he gets a slight knock on the head when playing.

No family history of skin trouble or asthma.

9.2.21. Cutaneous tests for milk, egg-white and yolk, potato, /

potato, rice, wheat, oat, beef all negative.

The child was not brought back though it seems probable that further tests would have discovered some sensitization.

Case No.15. Mrs E.B., aet. 27. Widow.

Keeps a saddler's shop.

Attended Skin Department, R.I.E.

Urticaria. At the end of 1917 had an eruption of urticaria on her waist. This was after eating chicken and tongue and was preceded by a feeling of sickness. Since then she has never been entirely free from urticaria. There are frequent exacerbations with quieter intervals. She can foretell an attack by a feeling of sickness but knows of no special article of diet that causes it. When the trouble began she was ordered a light diet of chicken, fish, etc., but without benefit. For two days, under the advice of Dr Norman Walker, she has been on milk only, and has felt much relief. Bowels regular, digestion good. Many carious teeth. Usually takes an ordinary diet but is very fond of tomatoes and bananas, and eats them all the year round. Has also a special fondness for carrots. She eats salmon and sole occasionally.

18.2.21/

- 18.2.21. Cutaneous tests for cheese, chicken, egg white and yolk, milk, lamb, almond, pork, barley, bean, beef, oat, onion, wheat, walnut - all negative.
- 21.2.21. Tests for potato, rice, halibut, haddock, herring, cocoa, tea, turnip, cabbage, horse dander - all negative.

Tomato and banana slightly + .

Carrot, salmon and sole + - .

She was instructed to avoid tomatoes, bananas, carrots, salmon and sole.

2.8.21. In reply to my enquiry she wrote.-

"Since my visit to you in February, I am almost rid of the rash. I have been eating tomatoes, etc. without any complaint.....
I was recently married."

It is difficult to say whether abstention from tomatoes, etc. or a happy romance was the beneficial factor in this case.

Case No.16. Mrs M.S., aet. 40.

Attended Skin Department, R.I.E.

Urticaria: duration 17 months.

Began in September 1919 when she was very run-down from nursing her husband through a long and serious illness.

The eruption is absent in the morning and comes out in the afternoons and during the night, chiefly on the back of the shoulders and to a lesser degree on the rest of the trunk and limbs. It causes much distress and insomnia.

She knows of no cause dietetic or otherwise for the origin of the urticaria.

She suffers from constipation.

As a child she could not touch eggs, as they caused immediate vomiting, but for the past four or five years she has been able to take them and they are a regular part of her diet.

She loathed milk as a child, and porridge always brought her face out in spots so she never takes it. Oatcakes she likes but does not think that they agree with her. She is sure that fish greatly aggravates her urticaria.

She is very sensitive to Mimosa flowers and is "scunnered" by the proximity of a cat. She occasionally suffers from "bronchial attacks" which last for several weeks and are characterised by loud wheezing, but she has not had asthma.

Her eldest brother suffered from asthma all his life. Two other brothers died in early manhood from diabetes mellitus.

1.3.21./

1.3.21. Had just lunched off mutton, potatoes and vegetables and urticarial wheals had as a consequence come out on back, chest and arms. Dermography was present. She stated that a "bun lunch" would not have been followed by an eruption.

Cutaneous tests for milk, chicken, pork, onion, wheat and potato - negative.

Cheese and sole + - .

Haddock, herring, lamb, egg yolk + .

Egg white and oat + + .

3.3.21. Has been on pure milk diet since 1.3.21 by orders of Dr Norman Walker. This has caused acute indigestion and vomiting and the urticaria has been much worse. Ordered a bread and butter diet.

7.3.21. Reports that she had had no nocturnal urticaria for three nights but has had a little in the morning. Indigestion improved.

Cutaneous tests for rice, salmon, barley, beef, milk, walnut, pine-apple, tea, cabbage, turnip, carrot, tomato, banana, plum, veal, cat's hair - all negative.

Celery + - .

Coffee + + .

Instructed to eliminate eggs, fish, coffee, oatmeal, /

oatmeal, mutton, cheese, and celery from her diet but otherwise to eat what she liked.

Treated for constipation.

14.3.21. Reports that she still gets a little urticaria but it is much less than formerly and she gets undisturbed nights.

1.8.21. Scarcely suffers at all from urticaria, is much improved in health, and full of gratitude for the relief she has obtained.

Case No.17. S.W., aet. 8, female.

14.3.21. For seven years has suffered from repeated attacks of an impetigenous eruption on face, back of wrists and hands, and on back of neck.

It is thought that there may be an urticarial basis to the impetigo.

4.3.21. Cutaneous tests for milk, egg white and yolk and oats all — .

8.3.21. Tests for wheat, pork, potato, rice, haddock, herring, lamb, onion, beef, barley, walnut, all — .

Case No.18. R.H., aet. 29. Machine repairer.

(?) Urticaria. His first attack was while serving in France in 1916, when he had an eruption of "blisters containing matter" on shoulders, knees, and hips. No pain or itching. Duration of attack - two months. Since then repeated attacks every few months alternating with quiet intervals. Digestion good. Ordinary mixed diet. Has not observed any article that causes exacerbation. Bowels and digestion normal.

14.3.21. Has some urticarial wheals on arms and body. Cutaneous tests for Oat, onion, almond, beef, pork, rice, haddock, herring, lamb, egg white, cheese - all negative.

Barley, bean, potato, egg yolk, salmon, wheat, milk, all + - .

21.3.21. Tomato, turnip, tea, cabbage, cocoa, carrot, coffee, banana, bean, turnip, potato, egg, milk, wheat - all negative.

I did not see the case again.

Case No.30. D.L., aet. 43. Draughtsman.

Attended the Eye Department, R.I.E., for
Angio-neurotic Oedema of right orbit
 and lip. The condition began 3 years ago without any
 obvious cause and has recurred off and on ever since.
 He goes to bed all right and wakes up in the morning
 with an eye bunged up or the privates much swollen.

He will have 3 weeks of successive swellings
 followed by an interval of about 3 weeks.
 Appetite good. "Eats anything", and has never
 noticed any connection with any article of food except
 that once an attack followed a supper of tinned salmon.
 Bowels regular.

23.7.21. Cutaneous tests for

Haddock ++.

Herring and sole +.

Halibut, strawberry, egg yolk + -.

Egg white, salmon, banana, tomato, cabbage,
 cheese, wheat, pork, potato, rice, barley,
 carrot, turnip, pea, bean, beef, oat, onion,
 tea, coffee - all negative.

10.9.21. A letter of inquiry as to his present con-
 dition ^{was} returned by the P.O., patient having
 changed his residence.

3. DERMATITIS.

Dermatitis venenata has already been referred to and it is not necessary to discuss it further, as there is no evidence of its connection with sensitization to foreign protein. It is however necessary to point out how closely it depends on individual idiosyncrasy to articles in common use, and the necessity for eliminating it in any case before diagnosing the idiopathic variety.

The idiopathic dermatitis which I shall discuss here is called by most authors by the term "Eczema". It is characterised by a catarrhal inflammation of the skin, originating without visible external irritation, and characterised in some stages of its evolution by serous exudation. In spite of much research into its etiology, this condition, though one of the commonplaces of Medicine, still remains one of its unsolved problems.

It is common in all climates and sex has no special influence though some observers claim a preponderance of cases in the male.

Seborrhoeic Dermatitis is a very common affection in infancy occurring especially during the period/

period of first dentition in breast-fed, as well as in bottle-fed babies. Puberty is the next period of life when dermatitis is specially liable to occur and it may then be associated with asthma and other conditions.

About the time of the menopause in both sexes there is again a greater liability to the affection, and it may be associated then with gout, rheumatism or other constitutional conditions, but Malcolm Morris¹⁴² does not regard these as more than accidental complications. On the other hand its association with asthma is so frequent, that some dermatologists have believed asthma to be in many cases simply an "Eczema" of the bronchial tubes just as they have ascribed the asthma that is associated with urticaria, to an urticarial eruption in the bronchi.

Of Dr John Thomson's¹⁴³ 100 cases of asthma in children, 26 had eczema in infancy.

The influence of the nervous system on the occurrence of dermatitis has long been known, and Morris¹⁴⁴ holds that "Under the influence of nerve shock and nerve exhaustion it may arise de novo in a previously healthy skin". Certain it is, that it is one of the diseases that occur in neuropathic families, and Leloir and Bulkeley regard it as simply

a/

142. *Diseases of the Skin* 6th Ed. p.307-307.

143. *Clin. Study & Treatment of Sick Children*. p.521

144. *Diseases of the Skin*. 6th Ed. p.300-301 et seq.

a tropho-neurosis. Hall considered it to be a reaction of the neuro-cutaneous apparatus to an external irritant such as cold, soap, dust, etc. Unna and his followers on the other hand maintained that eczema was always due to an infection with bacteria chiefly the staphylococcus.

Bender, Bockhart, and Gerlach from a series of experiments on themselves, came to the conclusion that inoculation of the skin with virulent cultures of staphylococcus pyogenes aureus and albus never produced "eczema" but that their toxins were capable of producing typical acute papular or vesicular dermatitis when applied to the skin for some hours with or without previous irritation of the skin. On the other hand Veillon, Reibich, and Warde have repeatedly found the contents of the clear vesicle of dermatitis to be sterile.^{144.}

It seems probable therefore that although the staphylococcus may not be the primary cause of dermatitis, it plays a very important part as a secondary infection in the development of the process, once it has originated.

This, then, was the general state of opinion on the subject of idiopathic dermatitis, when in 1910 at the annual meeting of the American Dermatological Association/

^{144.} Quoted by Malcolm Morris, "Dis. of the Skin" 6th Ed.

Association at Washington, Fordyce¹⁴⁵ made the suggestion that eczema, like urticaria, might be dependent on the anaphylactic state, and pointed out the frequency with which it originated from some septic focus such as an abrasion or boil. At the next annual meeting of the association he developed his theory and on the analogy of the dermatitis that develops on repeated exposure to formaldehyde or Rhus Toxicodendron, he suggested that individuals may become sensitized to the chemical products of pus organisms just as tuberculous patients are to tuberculin.

He thought that a severe vesicular eruption might possibly be due either to an unusual unidentified infection or to an accidental sensitization to bacterial or food proteins. With the introduction of the cutaneous test for sensitization, it was possible to apply it to Fordyce's hypothesis.

In 1916 C.J. White¹⁴⁷ reported the result of cutaneous tests in 64 cases of chronic "eczema". He used four test substances, viz.- (1) fat-free milk; (2) egg white; (3) salt-free butter; and (4) oatmeal water.

80% of his cases gave a + reaction to one or more test substances.

A/

145. "Infective eczematoid dermatitis - the possible influence of Anaphylaxis in Skin Diseases". Jour. Cut. Dis. 29: 129, 1911.

146. Jour. Cut. Dis. 30: 128, 1912.

147. Jour. Cut. Dis. 34: 57. (Feb.) 1916.

A year later he¹⁴⁸ reported on a second series of 107 patients tested with the same substances. Of this series 45% gave a + reaction.

In 1918 he¹⁴⁹ reported a series of cases of eczema in children which he tested with pure proteins and got + reactions in 66%.

In 1916¹⁵⁰ Strickler and Goldberg applied intradermal tests to 15 children suffering from "eczema" and got + reactions in 33.3%.

In the same year Strickler¹⁵¹ reported the result of intradermal tests in 46 cases of eczema, mostly in adults. He used 15 different test proteins and got + reactions in 74%, and stated that 50% of these were in greater or less degree benefited by change of diet as indicated in the reactions. He considered that "In eczema more than in any other disease protein skin tests were of value, a strong reaction holding out great hope of cure or improvement".

Talbot¹⁵² in a paper on "Eczema in childhood" stated that in a series of tests on 16 cases of eczema in infants and children, he got a + reaction to egg white in 87% and a few reactions to other proteins.

In/

- 148. Jour. Am. Med. Assoc. 68:81, Jan. 13, 1917.
- 149. Boston Med. & Surg. Jour. 178:5, Jan. 3, 1918.
- 150. Jour. Am. Med. Assoc. 66:249, 1916.
- 151. New York Med. Jour. 104:198, (July 29) 1916.
- 152. Med. Clin. N. Amer. 925, Jan. 1918.

In another paper he stated that in eczema of childhood, the proteins most commonly reacted to, are egg white and cow casein and that rice may also be concerned in sensitization. Chandler Walker¹⁵³ has reported 4 cases of eczema due to sensitization to air-borne proteins.

One case of eczema and asthma was sensitive to horse dander. Another case occurred in a horse-asthmatic as a result of an attempt to specific desensitization.

Other two were due to the pollen of Timothy grass and ragwood respectively.

A case has recently been reported of a woman whose dermatitis was traced to a guinea pig that occasionally sat on her shoulder. She was sensitive to its fur.

Howard Fox¹⁵⁴ tested 22 cases of eczema with horse dander and got a + — reaction in 3; 13 cases with dog's hair with a + reaction in one; and eight cases with chicken feather - all being negative.

These facts show that a small proportion of cases of dermatitis is due to sensitization to air-borne proteins.

Ramirez¹⁵⁵ tested 66 cases of eczema in patients of/

153. Jour. Amer. Med. Assoc. 70:897, Mar 30, 1918.

154. *idem*. 75:14. Oct. 2, 1920.

155. Quoted by Howard Fox & Fisher in J. A. M. A. 75:14, Oct. 2, 1920.

of 15 years old and upwards. 30% gave a + reaction, all to more than one protein.

Of 20 cases giving a reaction who were treated by the dietary restrictions indicated, 6 were cured, 9 improved, and 5 unimproved.

Howard Fox and Fisher in recording their own series of 60 cases of eczema, nearly all adults, report that 31.66% reacted to one or more proteins. They employed from 13 to 37 test proteins in each case, the average being 25.

¹⁵⁶Engman and Wander report that of their cases of eczema in infants 78% and of chronic general eczema in older patients 38% gave cutaneous reactions to one or more proteins. It is interesting to note that in the adult cases tested by Ramirez, Howard Fox, and Fisher the proteins of cereals and vegetables figure prominently among the positive reactions and egg has by no means the importance attached to it by Talbot, Schloss and others in the dermatitis of childhood.

¹⁵⁷ Foote records three cases of dermatitis in infants aged 8 months, $2\frac{1}{2}$ years, and 3 years respectively, each of whom gave a + reaction to egg. In two of them a previous attack of Dermatitis had recovered on exclusion of egg from the diet. The relapse/

156. *Arch. of Derm. & Syphil.* March 1921

157. *Internat. Clinics*. Vol. IV. Series 30. p. 212.

relapse in one case was due to the child being given cookies containing egg in the glaze. In the other case it was consequent on an egg having been accidentally broken over its head and face. The third case although not supposed to be getting egg, was being given biscuits which contained egg.

To sum up the observations of these investigators, we may say that.- (1) About 80% of cases of dermatitis in children give + reactions to one or more proteins as compared with about 30% of adult patients.

(2) A + reaction to egg is got in a very large proportion of children with dermatitis, while in adults the egg is much less frequently the toxic agent, and cereals, vegetables, and fruits are at least of equal importance with egg, oysters, and pork.

(3) The air-borne proteins are occasionally responsible for dermatitis and must not be over-looked.

The practical results of treatment based on positive reactions is frequently disappointing especially in adults. Four of Howard Fox and Fisher's cases who had given multiple + or +++ reactions failed to improve on the indicated diet. One of them got worse, while three, having improved under X-rays, did not relapse when they ate the foods to which they had reacted.

As/

As will be seen my own results in five children and seven adults have been largely negative and the benefit to the patients nil.

C H I L D R E N .

Case No.1. Douglas G., aet. 4.

Dermatitis Seborrhoeica. Chiefly on face and legs. Has had repeated attacks for 3 years. No domestic history obtained. Ordinary light diet in hospital.

27.12.20. Cutaneous tests for Cow's milk, egg white and yolk, oat, potato, wheat - all negative. Recovered quickly under ordinary treatment.

Case No.5. Christina C., aet. 7.

Dermatitis Seborrhoeica on scalp, face, ears and body - duration 4 weeks.

History - commenced with ringworm of scalp 8 months ago, following epilation by X-rays.

20.1.21. Cutaneous tests for milk, egg, oats, — .
Rice and wheat + . Her temperature rose to 100° a few hours after the tests.

21.1.21./

21.1.21. Tests for potato and herring — .

Tea + .

Turnip, carrot, haddock + — .

24.1.21. Tests for onion, pea, bean, tomato, barley,

coffee, banana, beef — .

This patient was put on a diet from which rice, wheat, tea, turnip, carrot, and haddock were excluded. As far as I know the diet was adhered to by the nursing staff, but in a busy ward it is hard to prevent sympathetic fellow-patients from surreptitiously supplementing a child's diet with biscuits and bread. In any case the child did not improve.

Case No.6. Thomas F., aet. 4.

Dermatitis Seborrhoeica, $3\frac{1}{2}$ years duration.

Was breast-fed till 20 months old.

Dermatitis commenced at 6 months and has continued more or less ever since.

Scalp, face, axillae, groins, all affected.

20.1.21. Cutaneous tests for Cow's milk, eggs, oat,

rice, wheat, rye — .

21.1.21. Tests for potato, turnip, carrot, herring,

haddock, tea — .

11.2.21./

11.2.21. Dermatitis has flared up again.

Tests for egg white, rice, wheat, onion,
beef, bean — .

Oats and lamb + — .

Porridge and mutton were excluded from the diet,
but no improvement resulted.

Case No.7. Agnes McK., aet. 2 years.

Dermatitis of 2 months duration on face,
body, lower abdomen and thighs.

History slightly suggestive of Dermatitis herpetiformis.

24.1.21. Tests for milk, egg, wheat, oat, potato — .

31.1.21. Tests for beef, lamb, haddock — .

Rice, egg white, chicken + — .

Patient recovered under ordinary treatment and went
home.

Case No.21. David S., aet. 14 months.

Dermatitis Seborrhoeica - duration 4 mos.

Breast fed for 7 months, since then on

Cow's milk, oat flour, soups, egg, and

potato. But he has had no egg or potato since he
first attended the R.I.E. 2 months ago, and only milk,
bread and butter for past month.

The/

The dermatitis commenced after an attack of diarrhoea. He has improved little, if at all, under treatment.

22.3.21. Tests for egg white and oats + — .

Milk, egg yolk, wheat, lamb, beef, potato — .

The mother was instructed to give the child an ordinary diet excluding eggs and oatmeal.

I was unable to follow up the case.

A D U L T S.

Case No.2. Mrs C. McI., aet. 64.

Dermatitis Seborrhoeica - 24 years duration with repeated admissions to hospital.

The dermatitis usually commences on scalp and spreads to trunk, groins and legs.

27.12.20. Tests for milk, oats, potato, egg white and yolk, wheat — .

31.12.20. Went home much improved and was not seen again.

Case No.3. Mrs H., aet. 68.

Dermatitis Seborrhoeica - head, trunk,

arms. Commenced 4 years ago and has had repeated attacks since then. Has an ordinary mixed diet including porridge and eggs, apples and bananas.

4.1.21/

- 4.1.21. Cutaneous tests for tea, herring, onion,
egg, milk — .
Oats + — .
- 6.1.21. " " Coffee, potato, beef, chicken
feather, goose feather,
dog hair — .
- 11.1.21. " " Rice, pork, lamb, bac. coli,
Staph. Aur. and Alb. — .
- 13.1.21. " " Plum, pineapple, strawberry,
tomato, banana, apple — .

Oatmeal was excluded from diet without any benefit.

Case No.4. Jas. W., aet. 19. Baker.

Dermatitis (Baker's) 6 months duration,
affecting forearms, elbow flexure, upper
arms, thighs. Had "eczema" of body at age of 7 but
has had no other skin trouble till present illness
commenced in flexures of elbows six months ago.

Has worked as a baker for 12 months.

Works with wheat flour, barley bran, sugar, and
cotton seed oil.

Takes an ordinary diet.

- 10.1.21. Cutaneous tests for rice, wheat, tea, coffee,
carrot, potato — .
- 11.1.21. " " Oats, milk, beef, haddock,
herring, onion — .

13.1.21./

- 13.1.21. Cutaneous tests for Barley, turnip, banana,
plum, and sugar — .
- 22.1.21. " " Wheat, wheat globulin,
proteose, gladein and gluten,
Staph. aur. — .
- 25.1.21. " " Cotton seed oil — .

He improved steadily under routine treatment and relapsed when he resumed work before being quite well.

Case No.9. W.K., aet. 52. Horse shunter on railway.
Dermatitis Seborrhoeica. Commenced 8 weeks
ago on scalp and spread over head and body.

No previous attack. Winter bronchitis for 20 years.
Chest emphysematous.

Has an ordinary mixed diet and knows of nothing that
upsets him.

Digestion good; bowels regular.

- 25.1.21. Cutaneous tests for egg white, beef, wheat,
rice, milk, turnip,
oat, tea — .
- 29.1.21. " " Egg yolk, haddock, herring,
lamb, cheese, pork, potato,
rice, onion — .

Case No.10. A. McC., aet. 19. Stoker.

Dermatitis Seborrhoeica 4 months dura-

tion. Commenced from a bruise on shin and gradually spread from there. Has patches on legs, body, arms and head.

General health good. Knows of nothing that upsets him.

28.1.21. Cutaneous tests for cheese, egg, oat, onion, pork, potato, rice, wheat, milk — .

31.1.21. " " Barley, bean, beef, lamb, haddock, herring, mackerel, Staphylo. Aur, Alb, Citr, and Streptococcus Viride — .

Patient recovered under routine treatment.

Case No.22. J.C., aet. 43. Shipbuilder.

Dermatitis (?Venenata) 5 mos. duration.

Commenced 5 months ago while working with iron, acids, cement, and various woods including teak; he developed an eruption on external aspect of fore-arms with marked swelling of face, the eyes being "bunged up" for 3 days.

Off work for nearly a month by which time he was nearly well and returned to work. A few days later had a severe relapse. Again practically recovered while/

while at home and relapsed once more on return to work.

Eosinophils 5.5%.

23.3.21. Cutaneous protein tests for

Milk, egg, haddock, herring, onion,
pork, potato, rice, beef, lamb,
wheat — .

The history of this case points to a dermatitis venenata. He was told to bring samples of sawdusts and acids from his ship-building yard but I did not see him again.

Case No.26. X.Y. Ex-soldier, aet. 22.

Dermatitis Seborrhoeica face and scalp

4 years duration. Always recovers when

a week or two in hospital and relapses when he goes home. No flowers in house. Dog and cat kept.

Does not do gardening or carpentry.

30.3.21. Cutaneous tests for

Oat, onion, pork, potato, rice,
salmon, cheese, egg, haddock,
herring, milk, lamb, sole, wheat,
barley, bean, beef, dog hair,
goose feather, Staph. Aur. — .

The case was not seen again. It was suspected that a disablement pension did not encourage recovery.

Case No.29. A.L., aet. 66. Miner.

Under the care of Dr J.V. Paterson
for Cataract.

Dermatitis Venenata from Boric Acid. Extremely
sensitive to Acid Boric or Atropine in conjunctiva.

After extraction of cataract some Boric lotion
was accidentally instilled into the conjunctiva and
an acute dermatitis resulted with oedematous swelling
of both eyes and forehead.

20.7.21. Eosinophils 10.5%.

Cutaneous tests on forearm with drop of
ordinary ophthalmic solutions of Atropine,
Hyoscine, and Acid Boric — .

4. DERMATITIS HERPETIFORMIS.

This is an obscure disease characterized by the multiformity and herpetiform grouping of the lesions; eosinophilia of the peripheral blood and skin lesions; distressing itching and burning sensation and a great tendency to recurrence. Patients are usually of a neurotic temperament and some shock or strain frequently is the exciting cause of the eruption.

The condition was believed to be due to an autogenous toxin which probably acts indirectly on the skin through the nervous system.¹⁵⁸

It has been expected by many that sensitization to foreign protein would be found to be the key to the condition but so far these hopes have not been justified by the results of cutaneous tests.

Engman and Wander¹⁵⁹ report constantly negative results with cutaneous tests. Howard Fox¹⁶⁰ indicates a similar lack of results.

I have tested one case with negative findings.

Case No. 25. D. McB., aet. 49. Cooper.

Dermatitis Herpetiformis - duration $2\frac{1}{2}$ years.

Typical/

158. Malcolm Morris. *Dis. of the Skin*. 6th Ed. pp. 151-153

159. *Arch. Derm. & Syph.* Mar. 1921.

160. *Arch. Derm. & Syph.* Nov. 1920. Discussion on papers by Lewis, Kighman & Michael.

Typical lesions. Ordinary diet.

Appetite and digestion good.

28.3.21. Cutaneous tests for

Oat, onion, pork, potato, rice,
salmon, cheese, egg, haddock,
herring, milk, lamb, sole, wheat,
barley, bean, beef — .

5. ERYTHEMA.

- (a) Erythema fugax has been ascribed to reflex irritation from teething, unsuitable food, and worms.

John Thomson¹⁶¹ considers that many of these cases are due to protein sensitization.

I have no cases or figures in support of this assertion.

- (b) Erythema multiforme is regarded by most dermatologists as a toxic condition and it has been hoped that sensitization to food or bacterial proteins would be proved to be the cause.

Fordyce¹⁶² suggested that the erythemata and especially erythema multiforme might be due to sensitization to bacterial protein from infection either of the tonsils or the alimentary canal.

However Engman and Wander¹⁶³ report no positive reactions to cutaneous tests and Howard Fox¹⁶⁴ indicates a similar experience. I have tested one case only, with negative result.

Case No.24./

161. "Clin. Study & Treatment of Sick Children", 3rd ed.

162. "The influence of Anaphylaxis in the toxic dermatoses"
Journ. Cut. Dis. XXX. 1912. 128.

163. Arch. of Derm. & Syphil. Mar. 1921

164. *idem*, Nov. 1920. Discussion on papers.

Case No.24. Mrs S., aet. 37.

Erythema multiforme bullosa.

Admitted on 14.1.21 a fortnight after the commencement of the disease. Had grouped pustular lesions on trunk and limbs. Nikolsky's sign. Eruption spread over whole body but she recovered and went home after a month in hospital.

There was never eosinophilia.

25.3.21. Returned with a threatening of recurrence.

Cutaneous tests for

Egg, cheese, haddock, herring,
milk, lamb, barley, wheat, pork,
potato, oat, onion, bean, beef,
rice. Strep. Vir. and Haemolyt.
Staph. aur. and alb. — .

It remains to record briefly notes on three other cases which do not fall under any of the above headings.

Case No.8. R.S., female, aet. 17.

Psoriasis Vulgaris - 6 years duration.

Worst in summer and usually clears up in the Winter-time, recurring in Spring.

25.1.21. Cutaneous tests for egg white, beef, wheat, rice, milk, turnip, oat, tea — .

29.1.21. Tests for egg yolk, haddock, herring, lamb,
bean, pork, potato, rice, onion, barley — .

Case No.20. E.G., aet. 30.

Pruritus Ani within 15 minutes of eating
cooked cheese. Uncooked cheese has
no effect.

21.3.21. Cutaneous test for cheese protein — .

Case No.28. C.M., aet. 31. Female.

Acne rosacea. Commenced at age of 15 and
has been present ever since in varying
degrees.

Oatmeal "heats her blood," bananas give
indigestion.

15.7.21. Cutaneous tests for

Egg, carrot, turnip, onion, tomato,
beef, lamb, banana, tea, oat, wheat,
barley, potato, cabbage, rice, milk — .

VII.

DESENSITIZATION.

Desensitization of the sensitized organism may be practised by many different methods. In effecting it the counsel of perfection is to prevent the further introduction of antigen until such time as the sensitization has worn off. This usually requires a period of from a few months to three years, but in certain cases, sensitization, once acquired, seems to last for a lifetime.

This method of desensitization by exclusion, is practicable in laboratory experiments, in some cases of human sensitization to horse serum, and in certain cases of sensitization to articles of food or airborne proteins. In many cases however, it is not a practical policy and more direct methods must be employed to effect our purpose.

In experimental sensitization in animals and in serum-therapy in man, advantage may be taken of the fact that within the latent period of ten to fourteen days, and also during the anergic period following anaphylactic shock, further doses of antigen can be administered/

administered with impunity. Slow and gradual introduction of antigen prevents anaphylactic shock in animals and in serum-sensitive human beings.

¹⁶⁵ Besredka utilizes this fact by dividing the total amount of serum to be given, into fractioned doses, which are injected every ten to twenty minutes in gradually increasing amount until the full dose has been administered.

¹⁶⁶ C.B. Ker advises injecting 0.5 cc. serum subcutaneously four hours before the main dose, and ¹⁶⁷ Tanner Hewlett recommends the rectal injection of 5 to 10 cc. of serum per rectum 12 hours before the therapeutic dose as a satisfactory precaution against anaphylaxis. It has been suggested that the ox as well as the horse should be utilized for the preparation of anti-toxic sera in order that ox-serum might be available for those who are potentially sensitive to horse serum. In the case of sensitization to proteins of food and air-borne substances, desensitization may be practised by subcutaneous injection of the specific antigen in gradually increasing sub-toxic doses every 5 to 7 days until tolerance has been established. This is well exemplified/

165. "Anaphylaxis et. Antianaphylaxis"

166. "Infectious Diseases" 2nd Ed.

167. "Manual of Bacteriology" 7th Ed.

exemplified in the method of inoculating with pollen extracts against hay fever. The greatest caution in dosage must be observed as serious affects may follow an excessive dose.

For food sensitization oral administration of the offending article is recommended by Schloss,¹⁶⁸ Talbot,¹⁶⁹ and others. In a case of egg sensitization for example, a daily dose of egg powder is administered in a gelatin capsule, commencing with 1 mgm. and working up to 3 to 6 mgms. daily.

Schloss has kept track for periods of from 3 to 7 years of 12 patients who were desensitized by this method and finds that all are now immune to the foods previously toxic to them.

Pagniez and Vallery-Radot¹⁷⁰ produce "Digestive anti-anaphylaxis" by ingestion of a very minute quantity of the offending protein one hour before a meal. This method, however, does not seem to lead to more than a temporary tolerance for the offending protein.

Milk has been employed to procure both specific and non-specific desensitization. Weil of Lyons¹⁷¹ uses injections of milk to desensitize babies who/

168. "Allergy in Infants & Children" p. 483.

169. Boston Med. & Surg. Jour. Aug. 29. 1918.

170. Annales de Mèd. Paris. 1920. XLII : 303.

171. Quoted by Coke. B. M. J. 13. 8. 21. p. 236.

who are intolerant of milk. L. de May¹⁷² treated 32 cases of uncontrollable vomiting in children by subcutaneous injection of cow's milk and Varney¹⁷³ reports marked improvement in 50% of cases of infantile eczema as the result of giving a small rectal injection of cow's milk every two or three days.

The effect in certain cases of thorough cooking of eggs, milk, and other offending food substances has been pointed out by Stokes and others.

D R U G S.

Adrenalin Chloride has a remarkable effect in preventing or relieving anaphylactic shock in animals. Its mode of action is unknown but it possibly depends on the occurrence in anaphylactic shock of a nervous inhibition of supra-renal function.

It is a valuable remedy in severe serum sickness in man; its dramatic effect in many cases of asthma and the urticarias has been mentioned; and it has been found to prevent the erythema and other toxic manifestations of Salvarsan, if given a few minutes before the injection.^{174.}

It/

172. Quoted by Freeman. *Lancet*. 31.7.20. p.235.

173. *Arch. of Derm. & Syph.* Nov. 1920. discussion on papers.

174. Hägeli, *Abstr. Jour. Amer. Med. Assoc.* 1917. II : 1743

It is useless if given by the mouth.

In certain people even a moderate dose produces syncope and severe tachycardia. It is wise therefore to begin with quite a small dose, - say 3 to 5 minutes of a 1 in 1000 solution.

Sodium Hyposulphite is stated by Lumière and Chevrotin¹⁷⁵ to prevent anaphylaxis if added in small amount to the serum before injection.

Sodium Chloride injected intravenously in doses of not less than 0.8 grm. per kilo, of body weight, has been found by Brodin, Richet, and Saint Girons¹⁷⁶ to prevent anaphylaxis in dogs.

Large doses of common salt have been found useful by some sufferers from migraine in warding off attacks.

Bile Salts injected intravenously have been found to prevent anaphylaxis by reducing surface tension.

Guanidin Salts are stated by Burns and Watson¹⁷⁷ to protect animals from anaphylaxis by producing a block in the cardio-vagal inhibitory system.

Atropine/

175. Académie des Sciences, Paris. Séance 18.10.20.

176. Revue de Médecine, Paris. 1920. 27:1.p.7.

177. Journ. of Physiol. L. N°7. p.421.

Atropine was shown by Auer and Lewis¹⁷⁸ in 1910 to prevent anaphylactic death in guinea-pigs by relaxing the spasm of the plain muscle of the bronchioles. It's action is on the vagus. This accords with the long-standing employment of "cures" for asthma which contained belladonna and similar drugs.

Injections of atropine give relief in some cases of asthma and Stokes pointed out its value in preventing the toxic reaction to the Salvarsan group of drugs.

I have used it in migraine without success.

Chloral, Chloroform and other general anaesthetics.

Chloral was found by Banzhof and Famulener¹⁷⁹ to prevent anaphylaxis, while morphine had no effect. Richet concluded that chloral and similar drugs "Have the general property of suppressing all nervous intoxication, probably because the chemical action of the anesthetic on the nerve cells, prevents the protoplasm of the neurone from entering into any other chemical combination".

The effect of chloral on a certain type of infantile convulsions has been alluded to.

Auto-serotherapy/

178. Jour. Exper. Med. 1910. XII. 151

179. Jour. Infant. Dis. 1910. VII. 577

Auto-serotherapy has come into use for the purpose of desensitization in recent times.

Achard and Flandin¹⁸⁰ in an article on Auto-serotherapy in hay fever, urticaria, etc., explain that in conditions in which the element of anaphylaxis is evident, the serum acquires crypto-toxic properties and can be used for purposes of desensitization. They commence with a subcutaneous injection of 0.5 cc. of the patient's own serum, following it in 12 hours with 1 cc., next day 1 to 2 cc., the third day 2 cc., and then 2 cc., every second or third day. They got good results with urticaria, angio-neurotic oedema and hay fever, but not with asthma. A more rough and ready method of applying the same principle is to withdraw 10 cc. of the blood from a vein and inject it subcutaneously or intramuscularly forthwith.

Durand¹⁸¹ has reported the cure of a severe case of migraine by this means and Nicolas, Gaté,¹⁸² and Dupasquier report one case of Prurigo ferox and one case of prurigo which resulted from Novarsenobillon, as having been cured by autohaemotherapy.

Bacterial Vaccines specific and non-specific have been employed by Danysz¹⁸³ and others in the treatment of conditions which they/

180. Bull. de la Soc. Méd. des Hôpitaux. Paris, May 21, 1920. 44: 19, p. 723

181. Bull. Soc. de Hyg. Jan 12, 1921

182. Ann. de Derm. & Syph. N° 3. 1921

183. "Origine, Evolution et traitement des Maladies Chroniques".

they regard as being due to sensitization to bacterial protein. It is really comparable to non-specific protein treatment with peptone.

Peptone Therapy the fact that suitable doses of peptone will produce in animals all the characteristic features of anaphylaxis, has been already mentioned. Biedl and Kraus¹⁸⁴ found that an injection of peptone desensitized dogs that had been sensitized to any specific antigen. This observation has been confirmed by numerous observers.

Peptone consists of a combination of primary proteoses, secondary proteoses, and peptone, the primary proteoses being the most important of the three from the therapeutic point of view. Proteose has been shown to be very feebly antigenic and it does not form complement-binding antibodies or precipitins. It's undoubted action as a non-specific desensitizing agent for almost any antigen, is explained on the theory that in the antigen-antibody reaction the antigen molecule is split, the toxic radical being closely similar in chemical architecture to/

184. *Wien. Klin. Woch.* N°11. quoted by Auld. *B.M.J.* 5-5-17.

185. *Ibid.* quoted by Auld. *B.M.J.* 14-5-21. p.696.

186.

to proteose.

¹⁸⁶
Dale in a private communication on the subject quoted by Auld says, "A dose of peptone, not itself large enough to produce any pronounced reaction, will weaken the response of a sensitized guinea pig to the sensitizing antigen, so that after such a dose it is possible to desensitize without producing any pronounced reaction" ---- "The specific desensitization would appear in part at least, to be due to the detachment of antibody from the cells".

¹⁸⁷
Auld in a series of very instructive articles on the use of peptone in the treatment of asthma and allied disorders, has indicated the principles which should govern its administration and his articles show that its value is being proved in an ever-widening sphere. He reports its successful use in asthma, hay fever, migraine, epilepsy, skin affections associated with asthma, and cyclic gastro-intestinal attacks. In his opinion peptone therapy is so satisfactory in all specific sensitizations, that its employment has rendered the performance of cutaneous tests largely an academic function. If his contentions stand the test of time and experience, it certainly/

186. Quoted by Auld. B.M.J. 14.5.21. p. 696.

187. B.M.J. 5.5.17; 20.7.18; 24.4.20; 14.5.21.

188. B.M.J. 13.8.21. p. 237.

certainly is likely that the troublesome skin-test technique will in a few years be as little used as is the opsonic index estimation by the vaccine-therapist of today. Auld thinks that results may be still further improved by employing peptones of animal or vegetable origin according as the sensitizing antigen is animal or vegetable.

In cases of sensitiveness to Peptone, he recommends the addition of a few drops of Lugol's iodine to the solution. This enters into chemical union with a fraction of the peptone molecule without otherwise affecting its value. Both Auld and Gow¹⁹²⁸ warn against excessive dosage of peptone. The latter recommends a preliminary intradermal test with the peptone solution. An excessive reaction indicates the necessity for cautious dosage.

I have recorded one case of peptone therapy under Migraine.

I cannot conclude this thesis without expressing my great indebtedness to Dr Norman Walker, whose clinical assistant I had the privilege of being, for giving me the opportunity of testing the patients who were under his care in the wards and out-patient department of the Edinburgh Royal Infirmary.

All/

All the cases of skin disease recorded in this thesis, with two exceptions, Nos. 29 and 30, were under his care. The emphasis that Dr Norman Walker lays on the important part played in diseases of the skin by idiosyncrasy to foods and other substances is wellknown through his lectures and writings. I am most grateful to him for permission to record the results of my tests in this thesis and can only express my regret that owing to various circumstances my investigations and records have been so incomplete.

I must also express my gratitude to Professor Meakins for his great kindness in demonstrating the cutaneous test to me and for placing his test proteins at my disposal until my own supply arrived from America.

I am also indebted to Dr J.S. Fowler and the staff of the Sick Children's Hospital for giving me the opportunity of testing a few cases under their care.
